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M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE
6723 BERTNER AVENUE
HOUSTON, TX 77030

Consulting reviewer:
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In this issue:

- **BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)** 1
- **DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS** 2-8
- **BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS** 9-10
- **CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS** 11-16
- **BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)** 17-26
- **SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)** 27
- **SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)** 28-32

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE20.3173/2:

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA. I. PROGRAM AND PRIMARY FINDINGS IN 45-69 YEAR OLD WOMEN.

Andersson I
Dept. Diagnostic Radiology, Preventive Medicine, Univ. Lund, Malmo Allmanna Sjukhus, S-21401 Malmo, Sweden
Acta Radiol [Diagn] (Stockh); 22(2):185-194 1981

A cross-sectional randomized screening with mammary radiography of 15,748 women aged 45 to 69 and living in Malmo for the detection of breast carcinoma is described. The detection rate of breast carcinoma was 7.5 per 1,000, 16% of the carcinoma being non-invasive and 43 invasive with a diameter of at most 10 mm. The overall rate of axillary metastases was 18%. The sensitivity of the radiography was 91.5%, the specificity 99.2% and the predictive value 47%. It is concluded that mammary radiography is an effective screening method for detecting early carcinoma. (Author abstract) (66 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. THE ROLE OF COMPUTED TOMOGRAPHY OF THE BRAIN IN THE INVESTIGATION OF BREAST CANCER PATIENTS WITH SUSPECTED INTRACRANIAL METASTASES.

Dearnaley DP, Kingsley DP, Husband JE, Horwich A, Coombes RC
Ludwig Inst. Cancer Res., Sutton, England
Clin Radiol; 32(4):375-382 1981

Computed tomography (CT) of the brain has been performed in 60 patients with breast cancer presenting with neurological symptoms suggestive of intracranial metastases, and the findings correlated with clinical features and Technetium (Tc) brain scan when available. Small size of the intracerebral metastases demonstrated by CT was clearly correlated with good clinical response to treatment, and CT was effective in detecting residual tumor. However, the varied CT appearance of intracerebral metastases did not allow differentiation from primary cerebral tumors in those patients with solitary lesions. Tc brain scan was abnormal in most patients with intracerebral metastases, but was less effective than CT in detecting multiple deposits; furthermore, skull deposits frequently made interpretation difficult. Neither test was effective in detecting meningeal infiltration. Careful CT examination of the skull overlying apparent superficial parenchymal lesions permitted the recognition of a group of patients with extradural extension of skull deposits. CT examination of brain increases diagnostic accuracy and provides important prognostic information in patients with intracranial metastases from breast cancer. (Author abstract) (15 Refs)

3. FLOW CYTOMETRY OF BREAST CARCINOMA: I. RELATION OF DNA PLOIDY LEVEL TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR
(c/o Melamed) Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 48(4):980-984 1981

Flow cytometry studies of the DNA distribution of tumor cells from 92 human breast cancers showed measurable aneuploidy (hyperploidy) in 85 cases (92%). The DNA ploidy values were unimodal in each case, but there was a bimodal distribution for the entire series. One group of tumors had a diploid or near diploid DNA distribution and a second group had ploidy levels from triploid to tetraploid or higher. The tumors with lower DNA ploidy (at or near diploid) tended to be histologically low grade, cytologically more orderly and estrogen-binding positive; those with higher DNA ploidy were more likely to be higher grade, more anaplastic, and estrogen-binding negative. (Author abstract) (27 Refs)

4. FLOW CYTOMETRY OF BREAST CARCINOMA: II. RELATION OF TUMOR CELL CYCLE DISTRIBUTION TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR
(c/o Melamed) Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 48(4):985-988 1981

Flow cytometry analysis of cell cycle distribution was carried out on acridine-orange-stained cell suspensions freshly prepared from carcinoma of the breast of 90 women, and compared with control, benign breast specimens from 10 women. There was a significantly greater proportion of cells in S (9.1% +-5.8) and G2 + M (8.0 +-6.0) phases of the cycle in breast cancer specimens than in the S (1.5% +-0.6) and G2 + M (2.5 +-0.9) phases of the cycle in benign, control specimens of breast tissue. Great variation was noted among the breast cancers, with medullary carcinomas having the highest percentage of cells in S + G2 + M, and papillary, tubular, colloid and well-differentiated duct carcinomas having the lowest. Tumors from premenopausal women classified as estrogen receptor negative had significantly more cells in S + G2 + M than did tumors from postmenopausal women that were estrogen-receptor positive. (Author abstract) (13 Refs)

5. CELL PROLIFERATION AND ITS RELATIONSHIP TO CLINICAL FEATURES AND RELAPSE IN BREAST CANCERS.

Gentili C, Sanfilippo O, Silvestrini R
(c/o Silvestrini), Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy
Cancer; 48(4):974-979 1981

The relationship between primary tumor proliferative activity and clinical and pathologic characteristics was analyzed in relation to menopausal status for 541 breast cancer patients. The thymidine-3H labeling index (LI) showed significantly higher median values in cancers from premenopausal (4.2%) and paramenopausal (4.2%) patients in comparison to that of cancers from postmenopausal (1.8%) patients. The LI was not generally correlated to tumor size. The only significant correlation was limited to tumors with negative axillary lymph nodes from premenopausal patients. The proliferative activity of primary tumors was neither correlated to the presence nor

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the extension of axillary metastasis. The prognostic significance of the primary tumor LI was assessed in 145 untreated patients with cancers without axillary metastases. A higher median value of LI was observed in tumors from patients who relapsed (5.7%) within 52 mo than in tumors from those who did not relapse (2%). However, the difference was statistically significant (p less than 0.01) in premenopausal patients, but not in postmenopausal patients. Similarly, a significantly (p less than 0.0005) higher rate of relapse (67.4%) was observed in patients with tumors that had a LI above the median value of 4.6% in comparison to that (0%) of tumors with a LI below the median value in premenopausal patients. No statistically significant relationship was observed between proliferative activity of the primary tumor and risk of relapse in postmenopausal patients. (Author abstract) (23 Refs)

6. HISTOLOGICAL GRADE AND EFFERENT VASCULAR INVASION IN HUMAN BREAST CARCINOMA.

Hartveit F, Thoresen S, Thorsen T, Tangen M

Dept. Pathology, Norwegian Cancer Society and Gade Inst., Bergen, Norway

Br J Cancer; 44(1):81-84 1981

Primary breast carcinomas (23) with axillary-node metastases that also showed tumor cells in the efferent nodal vessels, tended to be of higher histological grade than those (21) without efferent vascular invasion. Nuclear hyperchromatism and mitosis is the factor of importance to grading in this respect. This factor also differentiated between RE+ and RE- carcinomas in this material. (Author abstract) (14 Refs)

7. DETECTION OF RECURRENT BREAST CANCER.

Cowan JD, Kies MS

Oncology Service, Brooke Army Medical Center, Box 517, Beach Pavilion, Ft. Sam Houston, TX, 78234

South Med J; 74(8):910-912 1981

Most clinicians attempt to identify and treat recurrent breast cancer at the earliest sign of relapse. In an effort to better define the usefulness of commonly used clinical and laboratory tools in evaluating patients after mastectomy, we retrospectively analyzed 120 cases and reviewed the literature. One hundred fifteen sites of metastatic disease were identified in 55 patients, with bone, lung, liver, and skin most common. History and physical examination disclosed 66% of these metastatic events. Of 36 patients with probable bone involvement, 15 were identified by bone scan while asymptomatic. Of 31 patients with evidence of pulmonary metastases, 12 were entirely asymptomatic when identified with a screening chest roentgenogram. In contrast, 36 of 45 hepatic, cutaneous, lymphatic, CNS, and ocular metastases were suggested by purely clinical findings. We conclude that basic clinical skills (ie, history-taking and physical examination) are two most important means by which we identify patients with recurrent breast cancer. While chest roentgenogram and bone scan may uncover metastases in asymptomatic patients, liver function tests and radionuclide scans of brain and liver have very low yield in patients clinically free of organ involvement. (Author abstract) (20 Refs)

8. MULTIPLE BIOLOGICAL MARKERS AND BREAST CARCINOMA: A PRELIMINARY STUDY IN THE DETECTION OF RECURRENT DISEASE AFTER PRIMARY THERAPY.

Waalkes TP, Abeloff MD, Ettinger DS, Woo XB, Gehrke CW, Mrochek JE

Johns Hopkins Oncology Center, Baltimore, MD, 21205

J Surg Oncol; 18(1):9-19 1981

The use of a selected group of biological markers in breast cancer patients who are disease free but at risk of relapse after mastectomy has potential for detecting recurrent tumor before there is clinical evidence. In this preliminary study, multiple materials were serially analyzed in the body fluids of patients without overt tumor but receiving adjuvant chemotherapy because of positive axillary nodes at surgery. The total frequency of elevated levels was determined and compared for those patients who remained disease free, for those who subsequently relapsed, and for a third group of patients with proven metastases. Frequency of elevation was directly proportional to increasing disease. Although differences in the relative frequency of individual materials were observed, the same trends with increasing tumor burden were found. The results suggest that the serial measurement of biological markers has potential for indicating the presence of occult disease. A nucleus of biological markers to be considered should include carcinoembryonic antigen, urinary hydroxyproline/creatinine ratio for bone lesions, and gamma-glutamyltranspeptidase for liver involvement. (Author abstract) (45 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

9. MEASUREMENT OF PROGESTERONE RECEPTORS IN HUMAN BREAST TUMORS: COMPARISON OF VARIOUS METHODS OF ANALYSIS.

Namkung PC, Petra PH

Dept. Lab. Mediciney Dept., Univ. Washington Sch. Medicine, Seattle, WA, 98195

J Steroid Biochem; 14(9):851-854 1981

The measurement of estrogen and progesterone receptors in human breast tumors is important to the successful management of the patients. These receptors exist in two macromolecular forms that have different sedimentation coefficients: 4S and 8S. Progesterone receptors were measured simultaneously in freshly prepared tissue cytosols from 10 individual tumors by three methods: the single-saturating dose (SSD) analysis, the sucrose density gradient method, and the multi-point Scatchard plot analysis. All three methods agreed extremely well for the determination of total (4S + 8S) receptor concentration; there was no loss of receptor-binding activity during the time required for sucrose density gradient analysis. The two macromolecular forms of the receptor appear to have similar if not identical dissociation constants because receptor concentrations calculated by extrapolation of linear Scatchard plots are identical to those obtained from either the summation of 4S and 8S areas of the density gradients or the SSD analysis. All three tested methods can be used in clinical measurements of the progesterone receptor. (14 Refs)

10. PROGNOSTIC VALUE OF CONCANAVALIN A REACTIVITY OF PRIMARY HUMAN BREAST CANCER CELLS.

Furmansk P, Kirkland WL, Gargala T, Rich MA, Breast Cancer Prognostic Study Clin ical Associates
Dept. Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(10):4087-4092 1981

A prospective, double-blind study was carried out to determine whether reactivity with concanavalin A (Con A) of human breast cancer cells was related to early disease recurrence. Mammary epithelial cells were isolated from 138 primary human breast cancers. The cells were placed in culture, and their reactivity with Con A was determined with a hemadsorption assay in which human RBC treated with various concentrations of Con A were incubated with the test (mammary epithelial) cells in situ. The Con A half-max value was determined as the concentration of Con A at which approx 50% of the target cells adsorbed RBC. Con A reactivity of the tumors was classified as high or low (half-max value less than or equal to 30 or greater than 30 ug/ml, respectively). Patients were followed for 2 to 60 mo after primary surgery (median, 22 mo). Those patients having tumors that were highly reactive with Con A were at significantly greater risk of developing early recurrence of their cancers than were those patients with low-reactivity tumors. No correlation was found between Con A reactivity and the age of the patients, their menopausal status, the number of axillary lymph nodes infiltrated with tumor, the estrogen receptor content of the tumor, or the clinical stage of the disease. These data show that Con A reactivity is an independent discriminator for identifying those breast cancer patients who are at high risk of developing early recurrent disease. (Author abstract) (28 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

11. DIAGNOSIS OF BREAST CARCINOMA WITH THOMSEN-FRIEDENREICH (T) ANTIGEN AND HUMAN ANTI-T ANTIBODY.

Springer GF, Murthy SM, Desai PR, Wurtz K, Black S, Scanlon EF
Dept. Surgery, Northwestern Univ., Evanston, IL
Breast; 7(3):24-30 1981

Delayed-type skin hypersensitivity (DTH) to T antigen was measures in 102 patients with ductal breast carcinoma, 24 patients with lobular and two patients with tubular breast carcinoma, and 148 patients with benign breast diseases. Cell-mediated T antigen immunity was measured in vitro by leukocyte migration inhibition. T-specific immunoreactive structures were found on 93% of breast carcinoma tissues, all distant metastasis tissues, all cultured breast carcinoma-derived cell lines, on adenocarcinoma tissues from other sites, and on four out of six melanomas. T-specific structures were not detected in 29 of 31 benign breast lesions or any of four mammoplasty tissues. Patients showing apparent false positives had hyperplastic conditions, which were later rediagnosed as carcinomas. Data from patients after surgery suggest that T-specific DTH may be useful in monitoring treatment of breast cancer treatment, since DTH disappears in patients not showing recurrence of tumors. Apparently T-specific structures occur in normal tissues in a covered form. In adenocarcinoma tissues these structures are in an exposed, reactive form, which may serve diagnostic purposes. The T antigen may be useful in adjuvant therapy. (31 Refs)

12. NATURAL CYTOTOXICITY OF PERIPHERAL BLOOD LYMPHOCYTES AND REGIONAL LYMPH NODE CELLS IN BREAST CANCER IN WOMEN.

Cunningham-Rundles S, Filippa DA, Braun DW, Antonelli P, Ashikari H
Clinical Immunology and Tissue Typing Lab., Memorial Sloan-Kettering Cancer Center, 1274 York Ave., New York, NY, 10021
JNCI; 67(3):585-590 1981

Natural cytotoxicity was studied before surgery or other treatment in 83 women with primary, untreated breast cancer. Peripheral blood lymphocytes (PBL) and cytotoxicity of regional lymph node cell(s) (RLNC) were examined in a 4-hr 51Cr release assay against the target cell K-562. Results indicated that greater than one-third of breast cancer patients have more negative lymphocyte cytotoxic activity toward K-562 than do the other two-thirds. Similar results were observed for PBL of 25 patients found to have benign breast lesions. Of these patients, 23 had fibrocystic disease. The difference between these findings and findings with normal control lymphocytes studied in parallel was highly significant (p less than 0.001). The study of RLNC cytotoxicity in patients with breast cancer showed that 25% of the patients' RLNC had significant natural cytotoxic activity toward K-562. Incubation of RLNC with interferon in vitro before addition of labeled K-562 cells did not induce cytotoxicity in RLNC that did not have this activity initially. (Author abstract) (23 Refs)

13. LYMPHOCYTES INFILTRATING HUMAN BREAST CANCERS LACK K-CELL ACTIVITY AND SHOW LOW LEVELS OF NK-CELL ACTIVITY.

Eremin O, Coombs RR, Ashby J
Univ. Dept. Clinical Surgery, Royal Infirmary, Edinburgh EH3 9YW, Scotland
Br J Cancer; 44(2):166-176 1981

Lymphocytes infiltrating human primary mammary carcinomas lack ADCC and show low levels of natural cytotoxicity. The peripheral blood lymphocytes, however, show a variable but prominent level of cytotoxicity. Lymphocyte preparations from breast tumors, when mixed with autologous blood lymphocytes, significantly suppress their prominent killer- (K- and NK-) cell activities. (Author abstract) (34 Refs)

14. INCREASED DETECTION OF MAMMARY CARCINOMA CELLS IN MARROW SMEARS USING ANTISERA TO EPITHELIAL MEMBRANE ANTIGEN.

Dearnaley DP, Sloane JP, Ormerod MG, Steele K, Coombes RC, Clink HMcD, Powles TJ, Ford HT, Gazet J-C, Neville AM
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 44(1):85-90 1981

We have developed a technique for the immunocytochemical staining of marrow smears using antiserum to epithelial membrane antigen (EMA). This membrane component is confined to, but widely distributed in, epithelial tissues and tumors derived from them, and is strongly expressed by infiltrating breast carcinoma cells. Marrow aspirates from patients with both early and metastastic breast cancer have been examined, and the results of immunocytochemical staining compared with conventional cytology and histology. Staining with antiserum to EMA enabled us to detect small numbers of carcinoma cells, and increased the yield of positive samples. Furthermore, using this technique, we found malignant cells in the marrow of patients with primary breast cancer with no other evidence of metastastic disease. Thus immunocytochemical staining for

EMA may be of value in the detection of micrometastases in patients with primary breast carcinoma. (Author abstract) (13 Refs)

15. DISTRIBUTION OF HLA CLASS 1 ANTIGENS IN NORMAL HUMAN TISSUE AND IN MAMMARY CANCER.

Fleming KA, McMichael A, Morton JA, Woods J, McGee JO'D

(c/o McGee) Nuffield Dept. Pathology, John Radcliffe Hosp., Headington, Oxford OX3 9DU, England

J Clin Pathol; 34(7):779-784 1981

With a monoclonal antibody which reacts with all HLA Class 1 antigens it was found that these antigens are not uniformly distributed in all nucleated cells. Rather HLA Class 1 antigens are restricted in their distribution to lymphoid cells, endothelial cells of small vessels, and certain epithelia including mammary duct cells. These antigens were not detected on hepatocytes, specialized cells of the central nervous system, or on the tumor cells of 8 out of 17 human mammary cancers. Given the hypothesis that T cells only respond to foreign antigens on cells which share a common major histocompatibility antigen, these results imply that the T cell responses to viral infections of hepatocytes - for example, hepatitis B virus and the CNS - for example, subacute sclerosing encephalitis, are mediated through an antigen system other than HLA Class 1. The absence of HLA Class 1 antigen on many mammary cancer cells may be of prognostic significance if T cell modulation of tumor growth is mediated through this class of antigens. (Author abstract) (19 Refs)

16. DEMONSTRATION WITH MONOCLONAL ANTIBODIES OF AN UNUSUAL MONONUCLEAR CELL INFILTRATE AND LOSS OF NORMAL EPITHELIAL MEMBRANE ANTIGENS IN HUMAN BREAST CARCINOMAS.

Daar AS, Fabre JW

Nuffield Dept. Surgery, Univ. Oxford, John Radcliffe Hosp., Oxford OX3 9DU, England

Lancet; 2(8244):434-438 1981

Monoclonal antibodies to two differentiation antigens normally expressed on the membranes of breast epithelial cells were used in immunofluorescence studies on frozen sections of malignant breast tumors. It was demonstrated that most tumors did not express these antigens on their cell membranes, and it was possible to classify histologically indistinguishable tumors according to whether they expressed the antigens. The absence of these membrane antigens is likely to be a subtle indicator of cellular differentiation and to have metabolic and other functional implications for the tumor. The demonstration that otherwise indistinguishable tumors can be classified in this way therefore has obvious potential for clinical exploitation. In addition, it was demonstrated that the majority of the mononuclear cells in those tumors with intense mononuclear cell infiltrates expressed an antigen not normally found on mature lymphocytes and macrophages. (Author abstract) (11 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

17. CLINICAL PHARMACOLOGY OF TAMOXIFEN IN PATIENTS WITH BREAST CANCER: CORRELATION WITH CLINICAL DATA.

Fabian C, Sternson L, El-Serafi M, Cain L, Hearne E

Div. Medical Oncology, Univ. Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS, 66103

Cancer; 48(4):876-882 1981

Blood tamoxifen levels were determined for patients with metastatic breast cancer following initial and chronic dosing at bid 10 mg/m2 (m2) or a 20 mg/m2 single dose. Median time to response was 6 wk. Blood tamoxifen levels at that time were 10-fold greater than those obtained after an initial single dose; however, steady-state values were not achieved until 16 wk of chronic dosing. On a loading dose schedule of 40 mg/m2 bid for 7 days and 20 mg/m2 daily thereafter, blood levels greater than or equal to 10 mg/m2 bid steady-state values were reached in 1 wk. Levels drawn at peak and trough times suggest that tamoxifen may be given on a once-daily basis. Tamoxifen half-life was 9-12 hr after the initial dose and 7 days after chronic dosing. (Author abstract) (30 Refs)

18. PHASE II STUDY OF VINDESINE IN PATIENTS WITH METASTATIC BREAST CANCER.

Cobleigh MA, Williams SD, Einhorn LW

Univ. Illinois, Abraham Lincoln Sch. Medicine, PO Box 6998, Chicago, IL, 60680

Cancer Treat Rep; 65(7/8):659-663 1981

Twenty-six patients with far-advanced, refractory breast cancer were treated iv with vindesine (DVA) at a dose of 3 mg/m(2)/wk. In 21 evaluable patients there were 6 partial remissions. Four patients who did not respond after at least four doses of intermittent DVA received continuous-infusion DVA at a dose of 1.5 mg/m(2)/day x 2 every other wk; none responded. Five of the six responders had had disease progression on other vinca alkaloids. Leukopenia and neuromuscular toxicity were dose-limiting. (Author abstract) (11 Refs)

19. A PHASE II EVALUATION OF M-AMSA, 4'-(9-ACRIDINYLAMINO)METHANESULFON M-ANISIDIDE, IN PATIENTS WITH BREAST CANCER.

Currie VE, Howard J, Wittes R

Developmental Chemotherapy Service, Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

Cancer Clin Trials; 4(3):249-251 1981

A Phase II study of m-AMSA, 4'-(9-acridinylamino)methanesulfon-m-anisidide was carried out in 40 patients with metastatic carcinoma of the breast. The drug, at a dose of 120 mg/m2, was given as a single iv injection every 3 wk. One patient achieved a partial remission of 4 mo duration; three patients experienced minor response. This study suggests that the true major response rate of advanced breast cancer to m-AMSA given in this manner is less than 13% at the 95% confidence level. (Author abstract) (12 Refs)

20. MITOMYCIN C AND VINBLASTINE CHEMOTHERAPY FOR ADVANCED BREAST CANCER.

Konits PH, Aisner J, Van Echo DA, Lichtenfeld K, Wiernik PH
(c/o Aisner) Baltimore Cancer Res. Program DCT, NCI, 22 S. Greene St., Baltimore, MD, 21201
Cancer; 48(6):1295-1298 1981

Mitomycin C, 20 mg/m2 day 1, and vinblastine, 1.5 mg/m2 days 1 and 21 were administered iv to 31 patients with refractory previously treated advanced breast cancer. Courses were repeated every 6 to 8 wk when adequate hematologic recovery permitted. Thirty of the 31 patients were evaluable; 1 had a complete response and 11 had a partial response. Four patients had stabilization of their disease. There was a 12/30 (40%) response rate with a median response duration of 127 days (range 69-412 days). Toxicity included moderate to severe myelosuppression, infections, hemorrhage, neurologic symptoms, pulmonary toxicity and mucositis. In previously treated patients with poor prognosis, the combination of mitomycin C and vinblastine appears to be a worthwhile secondary treatment for metastatic breast cancer. (Author abstract) (14 Refs)

21. SURGICAL MANAGEMENT OF MULTICENTRICITY, NIPPLE-AREOLA INVOLVEMENT, AND BILATERALITY IN BREAST CARCINOMA.

Samhouri F, Block M, Kambouris A
19630 W. McNichols, Detroit, MI, 48219
Henry Ford Hosp Med J; 29(2):69-70 1981

A retrospective analysis of mastectomies for carcinoma performed between 1974 and 1978 was conducted in order to determine the incidence of multicentricity, bilaterality, and nipple-areola involvement. Multicentricity was found in 146/455 (51%), nipple-areolar involvement in 79/455 (17%), and bilateral cancers in 39/455 (8.9%). The need for an individual approach to the surgical treatment for breast cancer is stressed, and total mastectomy is recommended for invasive carcinoma until appropriate clinical trials assessing segmentectomy as definitive treatment for early breast cancer have been conducted. (12 Refs)

22. LIMITED SURGERY WITH OR WITHOUT RADIOTHERAPY FOR EARLY BREAST CARCINOMA.

Freeman CR, Belliveau NJ, Kim TH, Boivin JF
Dept. Radiation Oncology, Montreal General Hosp., 1650 Cedar Ave., Montreal, Quebec H3G 1A4, Canada
J Can Assoc Radiol; 32(2):125-128 1981

Between January 1971 and December 1978, 117 consecutive patients with unilateral early stage carcinoma of the breast were treated with limited surgery, with or without the addition of postoperative radiotherapy. Local excision alone was found to be inadequate treatment for T1 and T2 carcinoma of the breast. Local recurrence rates were also high in patients with T1 and T2 lesions treated by local excision plus relatively low dose radiotherapy. Local recurrence was, however, infrequent after partial mastectomy, and no local failures were observed after partial mastectomy plus postoperative radiotherapy to a dose of 5,000 rad in 5 wk. Morbidity with such treatment is minimal and cosmetic results are generally excellent. (Author abstract) (17 Refs)

23. MULTIMODAL TREATMENT FOR LOCALLY ADVANCED BREAST CANCER. RESULTS OF CHEMOTHERAPY-RADIOTHERAPY VERSUS CHEMOTHERAPY-SURGERY.

De Lena M, Varini M, Zucali R, Rovini D, Viganotti G, Valagussa P, Veronesi U, Bonadonna G
Istituto Nazionale Tumori, Via Venezian 1, Milan 20133, Italy
Cancer Clin Trials; 4(3):229-236 1981

In a prospective randomized study, the efficacy of two combined modality approaches (chemotherapy plus radiotherapy or chemotherapy plus mastectomy) was tested in a total of 132 women with locally advanced breast cancer. Chemotherapy consisted of adriamycin plus vincristine (AV) administered for three cycles before either local-regional modality and subsequently for seven additional cycles. Although a higher proportion of women achieved complete remission after mastectomy (100%) compared to women given radiotherapy (60%), the total response rate at the end of combined modality was identical (75%). There was no significant difference between the two treatment groups in terms of patterns of treatment failure, median duration of response, and total survival. Treatment was not influenced by menopausal or estrogen receptor status. Two patients of the surgical group showed adriamycin-induced cardiomyopathy after cumulative doses less than 500 mg/m2. The results of the present study failed to indicate that surgery per se improved the overall results, including local control, over radiotherapy in a combined modality setting. (Author abstract) (21 Refs)

24. A RANDOMIZED TRIAL COMPARING SURGICAL ADRENALECTOMY WITH AMINOGLUTETHIMIDE PLUS HYDROCORTISONE IN WOMEN WITH ADVANCED BREAST CANCER.

Santen RJ, Worgul TJ, Samojlik E, Interrante A, Boucher AE, Lipton A, Harvey HA, White DS, Smart E, Cox C, Wells SA
Div. Endocrinology, Milton S. Hershey Medical Center, Hershey, PA, 17033
N Engl J Med; 305(10):545-551 1981

A randomized clinical trial was used to establish whether surgical adrenalectomy is superior to a medical ablative approach to estrogen suppression using aminoglutethimide (AG) and hydrocortisone for the treatment of advanced breast cancer. Ninety-six postmenopausal or surgically oophorectomized women with inoperable, recurrent, or metastatic carcinoma of the breast were randomized to receive one of the two therapies. Before randomization, women were stratified according to disease-free interval, site of dominant disease, and estrogen-receptor status. Of 40 evaluable women treated with AG + hydrocortisone, 53% had objective responses, compared with 45% of 29 women undergoing surgery; the difference was not statistically significant. Objective tumor regression persisted for means of greater than 17.1 mo in the surgery patients and 17.2 mo in the medical group. No consistent differences were observed in the suppression of estrogens produced by the two therapies; in contrast, only AG + hydrocortisone preserved androgen production. Drug side effects include lethargy, dizziness, ataxia, skin rash, occasional hypothyroidism, and rare blood dyscrasias. While no women in the medical group had adrenal insufficiency, 5/29 in the surgical group had this problem at least once up to 2 yr after the operation. Given the demonstration that the surgical procedure is not superior to the medical, the medical approach could logically be chosen as a means to avoid major surgery and the required lengthy hospitalization in patients with metastatic breast carcinoma. (41 Refs)

25. DISEASE-FREE SURVIVAL AT INTERVALS DURING AND FOLLOWING COMPLETION OF ADJUVANT CHEMOTHERAPY: THE NSABP EXPERIENCE FROM THREE BREAST CANCER PROTOCOLS.

Fisher B, Redmond C, Wolmark N, Wieand HS
NSABP Headquarters, 914 Scaife Hall, Univ. Pittsburgh, Pittsburgh, PA, 15261
Cancer; 48(6):1273-1280 1981

Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials evaluating three different regimens of adjuvant chemotherapy [1-phenylalanine mustard (L-PAM), L-PAM + 5-fluorouracil (5-FU), L-PAM + 5-FU + methotrexate (MTX)] in patients with primary breast cancer and positive axillary nodes indicate that each regimen has significantly contributed toward achieving the initial goal of such therapy, namely to diminish or prevent treatment failure in all or major subsets of patients during the first 2 yr following operation when women are at greatest risk for a recurrence. Because of this hazard, chemotherapy was administered in all protocols for 2 yr. Findings were examined at the end of the 1st yr of therapy and at the termination of the 2nd yr for those who entered that yr of therapy disease-free in order to determine whether the 2nd yr of treatment contributed a benefit beyond that achieved from the 1st yr of therapy. A reduction in the incidence of treatment failure was evident in every subgroup of patients at completion of the 1st yr of therapy. There was evidence of added improvement during the 2nd yr of treatment in patients aged 49 yr or younger but not in those aged 50 yr or older. Despite the finding, it is not possible from these studies to be absolutely certain that a 2nd yr of therapy is or is not advantageous. Findings obtained to date from the three studies indicate that patients completing 2 yr of chemotherapy who are disease-free display a subsequent treatment failure rate that is no greater than that observed in untreated patients who survived 2 yr without recurrence. Consequently, any advantage in disease-free survival observed at completion of therapy has been subsequently sustained for several yr, suggesting this represents a real decrease rather than a postponement of treatment failure. (Author abstract) (8 Refs)

26. CLINICAL ESTIMATION OF THE GROWTH RATE OF BREAST CANCER.

Boyd NF, Meakin JW, Hayward JL, Brown TC
Ontario Cancer Inst., 500 Sherbourne St., Toronto M4X 1K9, Canada
Cancer; 48(4):1037-1042 1981

To test the ability of the patient's history to provide prognostically important information in breast cancer the authors used information prospectively collected by interview from 756 patients enrolled in a randomized controlled trial of adjuvant therapy. Classification of this information according to the principles of rate of growth created groups with substantial and statistically significant differences in survival. The survival differences created by classifying growth rate were comparable to those created by other prognostic factors, and independent of those created by stage, lymph node status or tumor grade. The patient's history in breast cancer is capable of providing reproducible prognostic information when it is suitably classified, and this information represents a useful addition to current methods of estimating prognosis in breast cancer. (Author abstract) (16 Refs)

SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)

27. THE COMBINATION OF THE ACUTE LEUKEMIA AND THE MAMMARY CANCER: REPORT OF THREE CASES.

Limon Villalas RA, Enriquez Cervantes C
Departamento de Oncologia, Hospital de especialidades del IMSS, Monterrey, N. L., Mexico
Rev Med Inst Mex Seguro Soc; 19(2):183-186 1981

Three patients with mammary cancer received different doses of irradiation. One to two yr later they developed acute leukemia. The possibility of the irradiation being the cause of the acute leukemia was discussed. There are many other reports in the literature of the leukemia, which followed the irradiation and one report of the four leukemia cases, which developed 1-11 mo after a primary neoplasia, although none of the women received irradiation. (24 Refs) (In SPA)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

28. ENHANCED CYTOSTATIC EFFECTIVENESS OF ANILINE MUSTARD AGAINST 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY TUMORS DURING REGRESSION IN RESPONSE TO OVARIECTOMY.

Benckhuysen C, Ter Hart HG, Van Dijk PJ
Dept. Biochemistry, Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Cancer Treat Rep; 65(7/8):567-574 1981

Sprague-Dawley rates bearing 7,12-dimethylbenz[a]anthracene (DMBA)-induce mammary tumors were treated with either of two aromatic alkylating agents, aniline mustard or melphalan, alone or combined with ovariectomy. Both drugs were applied once a wk for 8 wk. Eighty-four percent of the tumors responded to ovariectomy, 38% regressing completely and 46% regressing partially. Aniline mustard, though virtually ineffective as a single agent, appeared synergistic with ovariectomy: a 100% regression rate (72% complete, 28% partial) was observed for this combination. Treatment with melphalan was as effective as ovariectomy, but the combination of melphalan with ovariectomy was no more effective than either treatment alone. The end product of aniline mustard metabolism, p-hydroxyaniline mustard O-glucuronide, may be more extensively activated by beta-glucuronidase in hormonally regressing than in growing or stationary tumors. Intratumoral levels of beta-glucuronidase occurring in DMBA-induced tumors 4 days after ovariectomy were found to be similar to those in the aniline mustard-sensitive mouse plasma cell tumor ADJ/PC6. It remains to be more extensively studied whether an effect of endocrine treatment on tumor beta-glucuronidase levels, and possibly on intracellular distribution of enzyme, could be used therapeutically. An effectively scheduled cytostatic treatment (with a drug conjugate such as that formed metabolically from aniline mustard) in conjunction

with ovariectomy might be effective in the treatment of hormone-responsive breast cancer. (Author abstract) (29 Refs)

29. KINETICALLY DIRECTED COMBINATION THERAPY WITH ADRIAMYCIN AND X-IRRADIATION IN A MAMMARY TUMOR MODEL.

Braunschweiger PG, Schenken LL, Schiffer LM
Cancer Res. Lab., Allegheny Singer Res. Corporation, Allegheny General Hosp., Pittsburgh, PA, 15212
Int J Radiat Oncol Biol Phys; 7(6):747-753 1981

Cell kinetic perturbations induced by 200 rad x-irradiation (X) and 1 mg/kg ip adriamycin (ADR) separately or in combination were studied in T1699 mouse mammary tumors transplanted into male DBA/2J mice. The mitotic and thymidine labeling indices were determined in vitro at various intervals after separate or combined treatment; treatment efficacy was evaluated by tumor regrowth measurement in tumor-breeding mice. Kinetic results indicated that ADR and X each induced a 9-10 hr G2 block in cell progression. ADR and X given together increased S-phase transit time and G2 progression delay. Optimum sequences for subsequent ADR + X fractions were derived from the recovery kinetics after combined treatment: treatment schedules of up to four fractions were designed and assessed by the regrowth delay measurements. Greatest regrowth delay was seen in mice treated with ADR + X at 0, 15, 48, and 81 hr. Median survival for this group was 45 days. Thus, antitumor activity of ADR + X was enhanced by an inter-fraction interval that minimized proliferative recovery between fractions. (35 Refs)

30. FRACTIONATED RADIATION AND HYPERTHERMIA: EXPERIMENTAL AND CLINICAL STUDIES.

Overgaard J
Radiumstationen, Inst. Cancer Res., 44 Norrebrogade, DK-8000 Aarhus C., Denmark
Cancer; 48(5):1116-1123 1981

The effect of fractionated radiation and hyperthermia was experimentally studied in a C3H mammary carcinoma and its surrounding skin. Simultaneous radiation and heat (42.5 C -60 min) with one or five fractions gave thermal enhancement ratios (TER) of approx 2.5 in both tumor and surrounding skin, and no improved therapeutic effect was obtained. Five fractions of sequential treatment with heating 4 hr after radiation reduced the tumor TER to about 1.4, but when 72 were allowed between the fractions, no thermal enhancement of the skin was observed. Thus, an improved therapeutic ratio was observed. Clinically, the combined treatment was studied in 12 patients with 49 metastases from malignant melanoma treated with different schedules of radiation and hyperthermia (approx 43 C for 30 min). Simultaneous treatment with three fractions in 8 days gave TER values in the skin between 1.2-1.4, but a similar effect was found in the tumor. Three fractions of sequential treatment in 8 days did not produce any thermal enhancement of the skin response, but still presented an apparent gain of the tumor response, and so seemed to increase the therapeutic effect. Based on these findings, the strategy for further clinical use of combined hyperthermia and radiation is discussed. (Author abstract) (32 Refs)

31. THE HORMONAL REGULATION AND INTERACTION OF CONCANAVALIN A AND INSULIN BINDING IN R3230AC MAMMARY ADENOCARCINOMA CELLS.

Sorge LK, Hilf R
Dept. Biochemistry, Univ. Rochester Cancer Center, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
Biochim Biophys Acta; 676(2):187-198 1981

To investigate the effects of concanavalin A on insulin binding to R3230AC mammary carcinomas, initial experiments were performed to characterize binding of concanavalin A. Concanavalin A binding was found to be specific and saturable. Equilibrium binding experiments demonstrated that addition of low concentrations of concanavalin A enhanced the binding of concanavalin A, suggestive of positively cooperative interactions. Binding of concanavalin A was responsive to hormonal alterations; tumor cells from diabetic rats showed enhanced binding of [3H]concanavalin A and insulin compared to cells from intact rats and administration of insulin to diabetic rats returned concanavalin A and insulin binding to levels seen in controls. Incubation of tumor cells with concanavalin A prior to addition of 125I-labeled insulin resulted in a reduction of insulin-binding capacity; succinyl-concanavalin A did not affect binding of insulin. The percent inhibition of insulin binding by concanavalin A was highest at the lower insulin concentrations, providing a linearized Scatchard plot that yielded a calculated Kd value comparable to the low-affinity portion of the curvilinear Scatchard plot for insulin binding. The dissociation rate of bound insulin depended on receptor occupancy. Addition of concanavalin A after insulin binding reached equilibrium resulted in increased insulin binding at higher hormone concentrations, decreased rates of dissociation of insulin and a loss of the correlation between receptor occupancy and dissociation rates. Concanavalin A alone demonstrated an insulin-like effect on glucose transport, which in these tumor cells represents a decrease in transport of 3-O-methylglucose. These results suggest that binding of both concanavalin A and insulin to cells from this hormonally responsive neoplasm is under insulin regulation and demonstrates similar characteristics to those reported for a variety of normal cells. Furthermore, the interaction between concanavalin A and the cell membranes affects the affinity of the insulin receptor for insulin and appears to decrease the observed negative cooperativity. (Author abstract) (58 Refs)

32. TRANSFER OF ANTITUMOR IMMUNITY WITH RIBONUCLEIC ACID-CONTAINING SPLEEN EXTRACT OF IMMUNIZED ANIMALS. IN VIVO TRANSFER OF TUMOR IMMUNITY AGAINST MOUSE MAMMARY CARCINOMA.

Kurashige S, Mitsuhashi S
Coll. Medical Care and Technology, Gunma Univ., 3-39-15 Showamachi, Maebashi 371, Japan
Cancer Immunol Immunother; 11(3):189-193 1981

The combined effect of ribonucleic acid-containing spleen extract and live bacterial cells of an attenuated strain of Salmonella on tumor growth in recipient mice was studied. Mammary carcinoma Ca755 tumors were implanted in C57BL/6 mice, removed after 10 days, and retransplanted at appropriate times later. RNA was extracted from the spleens of mice that demonstrated resistance to the retransplantation (i-extract), and from spleens of untreated mice (n-extract). Additional mice were injected sc with 1 x 10(6) tumor cells/mouse, attenuated Salmonella enteritidis (SER: 1 x 10(5) cells/mouse), i-extract, and/or n-extract. Tumor growth was inhibited in mice receiving SER 6 days prior to tumor cell injection or i-extract 6 days after tumor cell injection. Inhibition of tumor growth was synergistically increased by SER given 6 days prior to, and i-extract given 6 days after, tumor cell injection. SER injected at or after the time of tumor cell injection had no effect. N-extract also had no effect. I-extract had no effect when injected prior to or at the same time as tumor cell injection. The results demonstrated presence of some factor which transfers immunity from donor to recipient mice. Injection of live attenuated SER stimulates a non-specific immune response which can act synergistically with the transferable factor. (13 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abeloff MD 8
Aisner J 20
Andersson I 1
Antonelli P 12
Ashby J 13
Ashikari H 12
Belliveau NJ 22
Benckhuysen C 28
Black S 11
Block M 21
Boivin JF 22
Bonadonna G 23
Boucher AE 24
Boyd NF 26
Braun DW 12
Braunschweiger 29
Breast Cancer P 10
Brown TC 26
Cain L 17
Clink HMcD 14
Cobleigh MA 18
Coombes RC 14
Coombes RC 2
Coombs RR 13
Cowan JD 7
Cox C 24
Cunningham-Rund 12
Currie VE 19
Daar AS 16
Darzynkiewicz Z 3
Darzynkiewicz Z 4
De Lena M 23
Dearnaley DP 14
Dearnaley DP 2
Desai PR 11
Einhorn LW 18
El-Serafi M 17
Enriquez Cervan 27
Eremin O 13
Ettinger DS 8
Fabian C 17
Fabre JW 16
Filippa DA 12
Fisher B 25
Fleming KA 15
Ford HT 14
Freeman CR 22
Furmansk P 10
Gargala T 10
Gazet J-C 14
Gehrke CW 8
Gentili C 5
Hartveit F 6
Harvey HA 24
Hayward JL 26
Hearne E 17
Hilf R 31
Horwich A 2
Howard J 19
Husband JE 2
Interrante A 24
Kambouris A 21
Kies MS 7
Kim TH 22
Kingsley DP 2
Kirkland WL 10
Konits PH 20
Kurashige S 32
Lichtenfeld K 20
Limon Villalas 27
Lipton A 24
McGee JO'D 15
McMichael A 15
Meakin JW 26
Melamed MR 3
Melamed MR 4
Mitsuhashi S 32
Morton JA 15
Mrochek JE 8
Murthy SM 11
Namkung PC 9
Neville AM 14
Olszewski W 3
Olszewski W 4
Ormerod MG 14
Overgaard J 30
Petra PH 9
Powles TJ 14
Redmond C 25
Rich MA 10
Rosen PP 3
Rosen PP 4
Rovini D 23
Samhouri F 21
Samojlik E 24
Sanfilippo O 5
Santen RJ 24
Scanlon EF 11
Schenken LL 29
Schiffer LM 29
Schwartz MK 3
Schwartz MK 4
Silvestrini R 5
Sloane JP 14
Smart E 24
Sorge LK 31
Springer GF 11
Steele K 14
Sternson L 17
Tangen M 6
Ter Hart HG 28
Thoresen S 6
Thorsen T 6
Valagussa P 23
Van Dijk PJ 28
Van Echo DA 20
Varini M 23
Veronesi U 23
Viganotti G 23
Waalkes TP 8
Wells SA 24
White DS 24
Wieand HS 25
Wiernik PH 20
Williams SD 18
Wittes R 19
Wolmark N 25
Woo KB 8
Woods J 15
Worgul TJ 24
Wurtz K 11
Zucali R 23

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BREAST CANCER

Diagnosis, Treatment, Pre-Clinical Biology

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In this issue:

- **BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)** 1-2
- **DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS** 3-8
- **BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS** 9-13
- **CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS** 14-16
- **BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)** 17-20
- **REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT** 21-22
- **SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY** 23-24
- **SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)** 25-31

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BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. CLINICAL BREAST EXAMINATION AS A SUPPLEMENT TO MASS SCREENING FOR CERVICAL CANCER.

Bostofte E, Berg O, Serup J

General Practitioners Southern Part Storstroms County, Bredevej 47 B, DK-2830 Virum, Denmark

Dan Med Bull; 28(3):100-101 1981

A program of mass screening for uterine cervical cancer has been conducted in the southern part of the Danish County of Storstroms since 1967. An initial screening period was conducted from 1967 to 1969 with a rescreening period from 1972 to 1974, and a supplementary clinical breast examination (inspection and palpation) to detect breast cancer was also carried out. A total of 18,577 women between the ages of 30 and 50 (54) were investigated (9,583 having participated in initial screening as well as rescreening), but only seven breast cancers were found (detection rate 0.4 per 1,000 women) compared with 102 breast cancers detected in other ways among the same women and registered in the region. The supplementary clinical breast examination was not found sufficient for breast cancer screening because the age grouping, screening interval and screening design was not optimal for this purpose. (Author abstract) (9 Refs)

2. BREAST CANCER POPULATION SCREENING BY SINGLE VIEW MAMMOGRAPHY WITH SELECTIVE CLINICAL EXAMINATION - A PILOT STUDY.

Thomas BA, Price JL, Boulter PS

Guildford Breast Screening Project, Jarvis Screening Centre, Stoughton Road, Guildford, Surrey, England

Clin Oncol; 7(3):201-204 1981

All women aged 45-64 registered with three group practices were invited to be screened for breast cancer by single view mammography. Sixty-two per cent (1,008) of the 1,634 women invited attended, and 123 were recalled for full assessment by clinical examination, further mammographic views and aspiration cytology of palpable lesions, because of major symptoms or a suspected mammographic abnormality. Thirty-four (3.4% of those screened) were referred for a surgical opinion; 15 underwent biopsy for a lesion proving to be benign, and 7 had carcinoma. Only two women had a clinically palpable lesion, and in all cases the nodes were tumor free. This compares with the 5 cases/1,000 detected in the neighboring population of the same age undergoing screening by single view mammography and clinical examination by the same team, but the costs are about half those incurred in the major project, being lb5 per woman invited or lb7-lb8 per woman screened including the review visit but excluding capital costs and accommodation. No women presented with breast cancer within a yr of screening by single view mammography. This screening procedure is of high sensitivity and specificity comparable with the 91% sensitivity and 98.7% specificity obtained with clinical examination in addition to single view mammography. (Author abstract) (2 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

3. CLINICAL, THERMOGRAPHIC, AND MAMMOGRAPHIC ASPECTS OF THE MAMMARY TEGUMENT.

Grumbach Y, Dieval M, Ducrocq C, Carton FX

Service de Radiologie B, Unite de Radiologie gynecologique obstetricale et mammaire, 124, rue Camille Desmoulins, 80030 Amiens Cedex, France

Rev Fr Gynecol Obstet; 76(7/8):529-542 1981

Superficial lesions of the breast are discussed in terms of clinical, thermographic, and mammographic findings. The anatomy of the breast (skin seam, areolar membrane, and sc fatty layer) is described. The systemic diagnosis of breast disorders is described: patient questioning, breast inspection, palpation, transillumination, thermography, mammography, xeroradiography, ultrasound, needle biopsy, and lesion excision. Tumors of various parts of the breast tegument, visible upon inspection, that could be responsible for abnormal mammography findings are described. These lesions include tumors of the skin seam (epidermal nevus, tuberous angioma, histiocytofibroma, and Recklinghausen disease) and areolar membrane (erosive adenomatosis, Paget's disease, folliculitis, and retractile galactophoritis). Benign tumors palpable in the breast tegument include sebaceous cysts, sc lipomas, cytosteatonecrosis, adipose necrosis, lipophagic granulomas, sclerosing adenosis, and lesions secondary to scar formation. Acute painful mammary syndromes described include vascular and (Mondor's disease and breast infarcts) and traumatic (hematoma) pathologies, inflammatory disorders (abscesses), benign tumors, and plasmocytic mastitis. Repercussions in the breast of cancer include skin infiltration and retraction. Repercussions in the nipple and areola of cancer are described. (22 Refs) (In FRE)

4. SIGNET RING CARCINOMA OF THE FEMALE BREAST: A CLINICOPATHOLOGIC ANALYSIS OF 24 CASES.

Merino MJ, Livolsi VA

Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar St., New Haven, CT, 06510

Cancer; 48(8):1830-1837 1981

Signet ring carcinomas of the breast have been separated recently as an aggressive subtype of breast cancer, distinct from mucinous (colloid) carcinomas. Twenty-four cases of signet ring breast cancer (2% of total breast cancers at the authors' institution) were analyzed. The authors' study indicates that histogenetically such lesions are derived from lobular, not ductal, cells since mucin patterns and ultrastructural features are shared. In addition, in each of our 24 cases, infiltrating lobular carcinoma was identified; in 11 of these (46%) lobular carcinoma in-situ (LCIS) was also noted. Signet ring carcinomas show an unusual metastatic pattern with a propensity to involve serosal surfaces and mimicking gastrointestinal disease or retroperitoneal fibrosis. These tumors are associated with a poor prognosis, with 60% of our 24 patients dead of disease at 7 yr. The distinctive clinical and pathologic features of signet ring carcinoma warrant separation of this group of tumors from other forms of breast cancer. (Author abstract) (25 Refs)

5. BIOCHEMICAL SUBGROUPING OF BENIGN BREAST DISEASE TO DEFINE PREMALIGNANT POTENTIAL.

Minton JP, Abou-Issa H, Elliot JB, Foecking MK, Roseman JM, Matthews RH
Dept. Surgery, Ohio State Univ., 410 W. 10th Ave., Columbus, OH, 43210
Surgery; 90(4):652-656 1981

To determine which subgroups of benign breast disease are likely to progress to malignant degeneration, a biochemical analysis of cyclic AMP (cAMP) was run on several samples of breast tissue. cAMP is elevated in a progressive fashion from normal breast tissue to fibrosis, cystic mastitis, ductular hyperplasias, and finally to carcinoma. Correlation of cAMP levels in breast lesions with histopathologic grading of increasing epithelial proliferation confirmed the concept that there are subgroups within those lesions that have greater malignant potential. Benign breast lesions with significantly higher cAMP levels, although still lower than those of cancer, must be considered at higher risk for eventual malignant change. (Author abstract) (19 Refs)

6. BIOLOGICAL CHARACTERISTICS OF BREAST CANCER AND THEIR CLINICAL RELEVANCE.

Silvestrini R, Daidone MG, Gentili C
Laboratorio di Cinetica Cellulare, Istituto Nazionale per lo Studio a la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy
Comment Res Breast Dis; 2:1-40 1981

The biology of breast cancer is reviewed. Kinetic and other biological characteristics of primary cancer are discussed. Overall kinetics are detailed, followed by the relationships between kinetics and menopausal status, patient age, estrogen receptor status, and tumor size. Relationships between labeling index and estrogen receptor status and levels are described. The relevance of biologic characteristics of primary cancer to axillary node status is discussed with respect to histologic grading, tumor kinetics, kinetics and estrogen receptor status, and kinetics and tumor size. The prognostic relevance of biological characteristics of primary cancer is related to lymph node involvement, histologic grading, estrogen receptor status, and kinetics and tumor size. Interpretation of clinical response on the basis of biological findings is discussed. (103 Refs)

7. BREAST PATHOLOGY, EMPHASIZING PRECANCEROUS AND CANCER-ASSOCIATED LESIONS.

Jensen HM
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA, 95616
Comment Res Breast Dis; 2:41-86 1981

Present knowledge, ideas, and speculations about breast pathology are reviewed. Discussion of the normal female breast includes gross anatomy, microarchitecture, and histology of the pubertal, mature, and aging breast; biology of the nonpregnant mature female breast with consideration of the terminal ductal lobular unit and formation and reabsorption of secretions; normal variations and the undefinable border between normal and abnormal conditions; benign histopathological changes in an occasional lobular unit; and atypical changes. Benign breast disease is discussed, including changes in multiple lobular units resulting in a palpable mass, and papillomas in ducts proximal to terminal ducts. Changes signifying risk for subsequent invasive cancer, precancerous lesions, ductal carcinoma in situ, precancerous versus cancer-associated lesions, and lesions judged cancer-associated are discussed. Pathologic and clinical aspects of invasive cancer are described. Pathological clues that a breast is at risk for cancer are summarized. (17 Refs)

8. PROGNOSTIC SIGNIFICANCE OF THE GROWTH RATE OF BREAST CANCER: PRELIMINARY EVALUATION ON THE FOLLOW-UP OF 196 BREAST CANCERS.

Galante E, Guzzon G, Gallus G, Mauri M, Bono A, De Carli A, Merson M, Di Pietro S
Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italia
Tumori; 67(4):333-340 1981

The doubling time (DT) of 196 consecutive breast cancers was studied by means of a double mammographic examination (av time between the 2 mammographies, 30 days) and calculated with the formula of exponential growth. On the basis of DT values the case series was divided into three groups of growth: fast (DT from 1 to 30 days), 31 cases (15.8%), intermediate (DT from 31 to 90 days), 84 cases (42.9%), slow (DT more than 90 days), 81 cases (41.3%). No relationship was found between growth rate and size of tumor, or menopausal status of the patient. After mastectomy fast and slow cases were equally distributed in the N- and N+ groups, whereas for the intermediate cases the N-:N+ ratio was 1:2. One hundred and thirty-four cases were followed for a period of 12 to 52 mo. Evaluation was done on the basis of the subdivision into N- and N+, and the latter group into N+ (1-3) and N+ (greater than 3). For N- tumors the course of the disease was apparently not affected by the growth rate. However, the case of fast growing tumors showed a higher proportion of recurrences with respect to N+ slow growing tumors. This difference was even more noticeable the higher the number of involved lymph nodes, but not statistically significant. The course of slow growing tumors was identical in the N- and N+ groups, but all the N+ tumors were subjected to adjuvant chemotherapy. (Author abstract) (19 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

9. INFLUENCE OF ESTROGEN RECEPTOR STATUS ON RESPONSE TO COMBINATION CHEMOTHERAPY FOR RECURRENT BREAST CANCER.

Mortimer J, Reimer R, Greenstreet R, Groppe C, Bukowski R
Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44106
Cancer Treat Rep; 65(9):763-766 1981

To determine the influence of cytoplasmic estrogen receptor (ER) status on response to chemotherapy among patients with recurrent breast cancer amenable to biopsy, we studied 65 patients who had ER determinations performed on metastatic lesions. The response to combination chemotherapy and duration of survival were determined in 49 of these patients who received cytotoxic chemotherapy as their sole modality of treatment. Compared to patients with ER levels less than 3 femtomols/mg, patients with an ER concentration greater than or equal to 3 femtomols/mg had a higher response rate (57% vs 21%, p less than 0.05) and a longer survival (35 vs 13 mo, p less than 0.0003). Some of the increased survival of the ER-positive patients was attributable to response to subsequent hormonal manipulations. These differences between ER-positive and ER-negative patients were lessened by redefining ER-positive as greater than or equal to 10 femtomols/mg. Nevertheless, at our institution patients with ER-positive metastatic breast cancer have a higher response rate to chemotherapy and survive longer than their ER-negative counterparts. (Author abstract) (17 Refs)

10. POSTABSORPTIVE URINARY HYDROXYPROLINE TEST IN PATIENTS WITH METASTATIC BONE DISEASE FROM BREAST CANCER.

Niell HB, Palmieri GM, Neely CL, McDonald MW
Section Oncology, Dept. Internal Medicine, Univ. Tennessee Center for Health Sciences, 800 Madison Ave., Memphis, TN, 38163
Arch Intern Med; 141(11):1471-1473 1981

Postabsorptive urine hydroxyproline (HYPRO) excretion ('spot' HYPRO test) was compared with the 24-hr urine excretion of HYPRO in 45 patients with breast cancer and 9 normal subjects on a low-gelatin diet. A good correlation was observed between the results of these two tests in both groups. Patients with skeletal metastasis showed a higher spot HYPRO value than those without bone involvement and the number of lesions by bone scanning correlated with the values of spot HYPRO. In 20 of 22 patients with bone metastasis followed up for 3 to 19 mo, spot HYPRO values correlated well with the evolution of bone disease. We conclude that the spot HYPRO test is a simple, inexpensive, and accurate method for the diagnosis and follow-up of patients with skeletal metastasis from breast cancer. (Author abstract) (16 Refs)

11. FAILURE OF ESTRADIOL IMMUNOFLUORESCENCE IN MCF-7 BREAST CANCER CELLS TO DETECT ESTROGEN RECEPTORS.

Mercer WD, Edwards DP, Chamness GC, McGuire WL
(c/o McGuire) Dept. Medicine, Div. Oncology, Univ. Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, 78284
Cancer Res; 41(11,part1):4644-4652 1981

An indirect immunofluorescence assay was used to detect estradiol in MCF-7 breast cancer cells to determine if the estradiol-specific fluorescence observed represented estrogen receptor-bound estradiol. Appropriate controls were used to demonstrate the immunological specificity of our assay procedures. Initial studies of estradiol binding in MCF-7 cells were performed at 20 C for 1 hr with different concentrations of estradiol. Cytoplasmic and nuclear staining were observed following treatment with 10 nM estradiol, but not with lower concentrations which were nevertheless still sufficient to saturate the estrogen receptor. The staining intensity increased with higher estradiol concentration, which is consistent with estradiol binding to lower-affinity binding sites. In order to further determine if estradiol binding by the estrogen receptor was being detected, we pretreated MCF-7 cells with 5 nM diethylstilbestrol at 37 C for 1 hr to translocate all the estrogen receptor to the nucleus and then administered estradiol at varying concentrations for 4 hr at 4 C. The estradiol was still primarily detected in the cytoplasm, although virtually all of the estrogen receptor was found to be present in the nucleus by standard [3H]estradiol binding assays. Additional immunochemical studies using sucrose gradient analysis to detect antibody-estradiol-receptor complexes clearly established that these complexes could not be detected. The present results suggest that, although immunocytochemical assays can specifically detect estradiol in MCF-7 cells, the estradiol is bound to lower-affinity binding sites rather than to the estrogen receptor. Saturation analyses of intact viable MCF-7 cells performed at 37 C for 30 min using [3H]estradiol at concentrations ranging from 0.1 to 93 nM revealed additional lower-affinity estradiol-binding sites besides the receptor, perhaps analogous to the Type II sites reported in the rat uterus and human breast cancers. (Author abstract) (45 Refs)

12. ESTROGENIC EFFECTS OF PHYSIOLOGICAL CONCENTRATIONS OF 5-ANDROSTENE-3BETA,17BETA-DIOL AND ITS METABOLISM IN MCF7 HUMAN BREAST CANCER CELLS.

Adams J, Garcia M, Rochefort H
Unite d'Endocrinologie Cellulaire Moleculaire, U 148 INSERM, 60, Rue de Navacelles, 34100 Montpellier, France
Cancer Res; 41(11,part1):4720-4726 1981

The compound 5-androstene-3beta,17beta-diol (ADIOL) has previously been shown to have a high affinity for the estrogen receptor and to translocate it to the nucleus in vitro and in vivo. This compound and related C19 delta5-steroids of adrenal origin have now been examined for their ability to induce the synthesis in MCF7 cells of an estrogen-dependent secreted glycoprotein (mol wt 46,000). Concentrations required for half-max induction were 2 nM for ADIOL and 500 nM for dehydroepiandrosterone (DHEA). Dehydroepiandrosterone sulfate showed weak inducing ability at concentrations of 1 uM or greater. The induction by ADIOL was unaffected by the presence of an aromatase inhibitor, and 5alpha-androstane-3beta,17beta-diol, which cannot be aromatized, also induced the mol wt 46,000 protein at low concentrations. When cells were exposed to 10 nM [3H]ADIOL, the cytosol and nuclear fractions contained [3H]ADIOL resistant to charcoal adsorption. The bound [3H]ADIOL in the cytosol and nucleus was displaceable by 17beta-estradiol and tamoxifen, suggesting that it was binding to the estrogen receptor. [3H]ADIOL was metabolized to its 3beta-sulfate, which was excreted into the medium, and to [3H]DHEA, which was found in the cells and the medium as free DHEA and its 3beta-sulfate. [3H]DHEA was also metabolized by the cells to its 3beta-sulfate, to free ADIOL, and to the 3beta-sulfate of ADIOL. We conclude that: (a) ADIOL is effective as an estrogen in MCF7 cells at a concentration of 2 nM, which is within the range found in the blood of normal women; and (b) sulfurylation is a major route of inactivation of 3beta-hydroxy delta5-steroids in MCF7 cells. (Author abstract) (31 Refs)

13. DETECTION OF HUMAN PLACENTAL LACTOGEN IN SERA AND TUMOURS OF PATIENTS WITH FIBROADENOMA OF BREAST.

Sheth NA, Adil MA, Suraiya JN, Sheth AR
Cancer Res. Inst., Parel, Bombay 400 012, India
Br J Cancer; 44(2):258-261 1981

While human placental lactogen (hPL) has been reported associated with malignant tumor, a study is presented which shows its presence in sera of 9/30 women with fibroadenoma of the breast while it was not detected in 30 normal non-pregnant women and 30 normal men. A sensitive radioimmunoassay was used for determination of hPL in tumor extracts and pre- and postoperative sera from patients. In a study of tumors from 21 patients, 9 extracts were positive for hPL. These nine patients (6 with unilateral and 3 with bilateral tumors) also showed hPL in preoperative sera. Twelve other patients (9 with unilateral and 3 bilateral tumors) showed no circulating hPL. Postoperative sera from seven of the nine patients with hPL in their tumors and preoperative sera became negative for hPL 1 wk to 6 mo after excision of fibroadenoma. In the case of bilateral tumors, the presence of hPL in both breasts suggests the possibility of a common factor governing ectopic secretion in both sites. The study indicated a greater production of hPL than beta human chorionic gonadotropin (beta-hCG) in sera of patients with fibroadenoma of the breast. These reports suggest a key role for hPL in the etiology of human benign breast tumors. (13 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

14. SIGNIFICANCE OF SERUM CONCENTRATIONS OF CARCINOEMBRYONIC ANTIGEN, FERRITIN, AND CALCITONIN IN BREAST CANCER.

Bezwoda W, Derman D, Bothwell T, MacPhil P, Levin J, De Moor N
Dept. Medicine, Medical Sch., Hospital St., Johannesburg, S. Africa
Cancer; 48(7):1623-1628 1981

Serum concentrations of carcinoembryonic antigen (CEA), ferritin, and calcitonin were measured in 107 patients with breast cancer, 80 of whom had overt or occult metastatic disease. CEA and ferritin values were statistically higher in those patients with metastases. In contrast, there was no correlation between calcitonin concentrations and the stage of the disease. All 27 subjects with CEA concentrations greater than 80 ug/liter and 32 of 40 with values between 41-80 ug/liter had metastatic disease. Ferritin was a definite but less sensitive discriminator, with metastatic disease present in all nine patients having concentrations greater than 400 ug/liter. Such metastases were invariably hepatic. When the two measurements were used as a combined discriminant, the diagnostic accuracy increased somewhat. All 32 patients with a CEA concentration greater than ug/liter and/or a ferritin concentration greater than 400 ug/liter had metastatic disease; the same was true for 32 of the 42 subjects with CEA concentration between 41-80 ug/liter and/or a ferritin concentration between 200-400 ug/liter. The measurements and prognostic value, both when assessed alone and together, with a median survival from the time of study significantly shorter in those with the highest values. (Author abstract) (23 Refs)

15. VALUE OF CARCINOEMBRYONIC ANTIGEN DETERMINATION IN MAMMARY CANCER.

Carrion P, Avila C, Massieu C, Curto M
Seccion Oncologia Medica, Centro Especial 'Ramon y Cajal', Madrid, Spain
Oncologia; 6(4):14,17-18,20-21 1981

Carcinoembryonic antigen (CEA) determination for early diagnosis of relapse after mastectomy and for monitoring effects of hormone and/or chemotherapies is evaluated. Of 140 mammary cancer patients, 9 with localized cancer were tested before and after surgery (Group I), 79 with localized cancer were tested 1, 3, 6, 12, and 24 mo after surgery (Group II), and 52 with advanced cancer (5 having distant metastases) were tested 10-21 days after the end of therapy (Group III). All patients received Halsted or Patey radical mastectomy; axillary adenopathies were examined histologically. Lymph node-positive patients received polychemotherapy and antiestrogen therapy for 6 mo. Patients with metastases were treated with different hormone therapy and chemotherapy. In Group I five patients exhibited elevated CEA which became normal after surgery, but later three of them developed metastases. In Group II 67 patients remain clinically free of disease, although 10 had elevated CEA values (greater than 50 mg in 2 cases). The remaining 12 patients developed metastases although CEA was normal in 8 and elevated in 4; 11 of the patients had axillary metastases with greater than 4 positive lymph nodes. In Group III 33 patients had elevated CEA (greater than 25 mg in 25 cases). CEA was elevated in 100% of hepatic, 83.3% of lung, and 72.2% of bone metastasis cases. Hormone therapy and/or chemotherapy was monitored in 25 patients; 80% of remissions and relapses could be followed by CEA. (12 Refs) (In SPA)

16. COMPLEMENT. EVALUATION OF SOME COMPLEMENT FRACTIONS IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY.

Ignesti C, Lenzi L, Salvadori D, Innocenti V, Baroncelli C, Casadei BM
Laboratorio di Analisi Chimico-Cliniche e Microbiologia, Ospedale Provinciale 'Misericordia e Dolce' di Prato, 50047 Prato (Firenze), Italy
Quad Sclavo Diagn; 17(2):152-163 1981

Cancer patients (20 men, 110 women; 92 having mammary cancer) were divided following disease evolution into the following groups: localized, progressive, complete remission, partial remission, or stationary. Total complement values were obtained through determinations of hemolytic activity; determinations also were carried out for the fractions C3, C4, C3 activated (C3act), and C1q. Healthy controls consisted of 40 men and 35 women. Blood samples were obtained from all test subjects before chemotherapy was started, 8 days later in 20 cases, and 30 and 60 days later in 40 cases. The hemolytic activity was decreased in all cancer patients, but it was significantly decreased only in those with complete remission. Levels of C4 and C1q in the cancer patients were comparable to those of corresponding fractions in the controls. The C3act levels were increased in the patients with complete or partial remission. The authors found that complement activity was triggered through classic or alternative means, caused by antigen-antibody complexes or inflammatory processes, according to increase or decrease of tumor mass. (14 Refs) (In ITA)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

17. VINDESINE IN THE TREATMENT OF REFRACTORY BREAST CANCER: IMPROVEMENT IN THERAPEUTIC INDEX WITH CONTINUOUS 5-DAY INFUSION.

Yap HY, Blumenschein GR, Bodey GP, Hortobagyi GN, Buzdar AU, DiStefano A
Dept. Medicine, Medical Breast Service, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer Treat Rep; 65(9):775-779 1981

Sixty patients with metastatic breast cancer refractory to prior doxorubicin combinations were randomized by performance status, dominant disease site, and number of involved organ sites to receive vindesine either as a bolus injection of 3-4 mg/m2 iv every 10-14 days or as a continuous 5-day infusion of 1-1.2 mg/m2/day every 21 days. There were 2 patients with partial responses (7%) and 6 with stable disease among the 26 evaluable patients who received bolus injections. Of the 25 evaluable patients who received continuous infusions, 7 achieved a partial response (28%) and 11 had stable disease (0.001 less than p less than 0.005). Thirteen patients, after failing to respond to bolus vindesine, were given continuous infusions. Of these, 11 were evaluable and 4 had partial responses (36%). Responses were seen in all organ sites of involvement, with response duration ranging from 2 to 9+ mo. Side effects included nausea, vomiting, stomatitis, constipation, neuropathy, fever, and myelosuppression. Except for myelosuppression, which was more evident with the continuous infusion schedule, no significant difference was seen in the frequency of side effects encountered with the two schedules. These results confirmed that there is an improved therapeutic index for vindesine when it is given as a continuous 5-day infusion. (Author abstract) (15 Refs)

18. ONE-DAY VATH (VINBLASTINE, ADRIAMYCIN, THIOTEPA, AND HALOTESTIN) THERAPY FOR ADVANCED BREAST CANCER REFRACTORY TO CHEMOTHERAPY.

Hart RD, Perloff M, Holland JF

(c/o Holland) Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, 100th St. and 5th Ave., New York, NY, 10029

Cancer; 48(7):1522-1527 1981

Twenty-nine postmenopausal patients with metastatic breast cancer refractory to conventional combination chemotherapy underwent treatment with a combination of vinblastine, Adriamycin, triethylene thiophosphoramide (thiotepa) and Halotestin given once every 21 days. Thirteen patients (45%) responded with a greater than 50% regression of measurable tumor. Responses occurred in 9 of 12 patients (75%) with visceral dominant disease and were recognized in 4 of 15 (27%) with osseous dominant disease (another 5 improved for a total improvement of 60%). The median duration of response was 11 mo. The median survival times were 16 mo for responders and 8 mo for those with progressive disease. Response rate was not affected by age, number of yr after menopause, number of metastatic sites involved, or number of systemic treatment modalities previously used, but may have been adversely affected by late stage at original diagnosis, short time from diagnosis, poor response to primary chemotherapy, and dose modification. This combination of drugs is a convenient, tolerable, and effective regimen for treating breast cancer refractory to primary chemotherapy regimens currently in use. (Author abstract) (29 Refs)

19. REVERSIBLE BRACHIAL PLEXOPATHY FOLLOWING PRIMARY RADIATION THERAPY FOR BREAST CANCER.

Salner AL, Botnick LE, Herzog AG, Goldstein MA, Harris JR, Levene MB, Hellman S

Joint Center for Radiation Therapy, Harvard Medical Sch., 50 Binney St., Boston, MA, 02115

Cancer Treat Rep; 65(9):797-802 1981

Reversible brachial plexopathy has occurred in very low incidence in patients with breast carcinoma treated definitively with radiation therapy. Of 565 patients treated between January 1968 and December 1979 with moderate doses of supervoltage radiation therapy (av axillary dose of 5,000 rad in 5 wk), 8 patients (1.4%) developed the characteristic symptoms at a median time of 4.5 mo after radiation therapy. This syndrome consists of paresthesias in all patients, with weakness and pain less commonly seen. The symptom complex differs from other previously described brachial plexus syndromes, including paralytic brachial neuritis, radiation-induced injury, and carcinoma. A possible relationship to adjuvant chemotherapy exists, though the etiology is not well-understood. The cases described demonstrate temporal cluste ring. Resolution is always seen. (Author abstract) (26 Refs)

20. FINDINGS FROM NSABP PROTOCOL NO. B-04: COMPARISON OF RADICAL MASTECTOMY WITH ALTERNATIVE TREATMENTS. II. THE CLINICAL AND BIOLOGIC SIGNIFICANCE OF MEDIAL-CENTRAL BREAST CANCERS.

Fisher B, Wolmark N, Redmond C, Deutsch M, Fisher ER, Participating NSABP Investigators

NSABP Headquarters, 914 Scaife Hall, 3550 Terrace St., Pittsburgh, PA, 15261

Cancer; 48(8):1863-1872 1981

Findings from 1,665 women with primary breast cancer, treated at 34 NSABP institutions in Canada and the United States, have failed to demonstrate that patients with medial-central tumors had a greater probability of developing distant metastases or dying than did those with lateral tumors despite the greater incidence of internal mammary (IM) node involvement when tumors are medial-central in location. A comparison of patients with similar clinical nodal status and tumor location who were treated either by radical mastectomy (RM) or by total mastectomy plus radiation therapy (TM + RT) failed to indicate that radiation of IM nodes reduced the probability of distant treatment failure (TF) or mortality. When findings from patients having equivalent clinical nodal status and tumor location treated by TM alone or TM + RT were compared, it was found that the addition of RT failed to alter the probability of the occurrence of a distant TF or of death. This was despite the fact that in the nonradiated group two putative sources of further tumor spread, ie, positive axillary and IM nodes, were left unremoved and untreated. The findings provide further insight into the biologic significance of the positive lymph node and confirm our prior contention that positive regional lymph nodes are indicators of a host-tumor relationship which permits the development of metastasis and that they are not important instigators of distant disease. (Author abstract) (14 Refs)

REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT

21. TOTAL MAMMARY ADENECTOMY WITH HISTOLOGIC EVALUATION AND IMMEDIATE RECONSTRUCTION.

Dinner MI, Labandter HP

Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH, 44106

Plast Reconstr Surg; 68(4):505-509 1981

Accurately performed, the operation described will approach total breast ablation, thereby providing the selected group of patients with the max possible protection against the development of carcinoma. This is the ultimate goal of elective prophylactic mastectomy. It is hoped that after 10 to 20 yr of reevaluation and close follow-up we shall know the answers to these uncertainties and thereby justify or discard the operation. (Author abstract) (16 Refs)

22. TOTAL MAMMARY ADENECTOMY WITH HISTOLOGIC EVALUATION AND IMMEDIATE RECONSTRUCTION. DISCUSSION.

Pennisi VR
Subcutaneous Mastectomy Data Evaluation Center, Saint Francis Memorial Hosp., Sa n Francisco, CA, 94109
Plast Reconstr Surg; 68(4):510-511 1981

Prophylactic total mastectomy followed by a subpectoral implant is discussed. Sc mastectomy is successful if the surgeon removes all visible breast tissue and if the pathologist does not overlook an invasive cancer in the excised specimen. Only 6/1,200 sc mastectomy patients later developed cancer. Use of polyurethane-covered silica gel implants to prevent capsular contraction is recommended. (5 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

23. CHARACTERISTICS OF FAMILIAL BREAST CANCER IN SWEDEN: ABSENCE OF RELATION TO AGE AND UNILATERAL VERSUS BILATERAL DISEASE.

Adami HO, Hansen J, Jung B, Rimsten A
Dept. Surgery, Univ. Hosp., S-750 14 Uppsala, Sweden
Cancer; 48(7):1688-1695 1981

A case-control study was conducted to examine the hypothesis that familiality in breast cancer is a heterogeneous entity. A study of 1,330 women, recently diagnosed as having breast cancer, compared, by paired sampling from a population register, the same number of age-matched women without a history of breast cancer. Data obtained by mailed questionnaires revealed a familial history in a first-degree relative in 149 patients and 90 controls (standardized relative risk/SRR/ = 1.7). The figures for second degree relatives were 115 and 81, respectively (SRR = 1.5). A detailed analysis of age at diagnosis and the occurrence of bilateral disease in the probands and their first-degree relatives with breast cancer failed to confirm any significant trend towards characterization of familial cases by early occurring or bilateral disease. The SRR for breast cancer in a first-degree relative was 1.7 for women with unilateral disease and 2.2 for those with bilateral. A slightly higher but nonsignificant relative risk was found for women diagnosed before (SRR = 2.4) than after (SRR = 1.7) 50 yr of age. Familial cases did not run a higher risk of developing bilateral disease than nonfamilial -6 and 5%, respectively. No patient or control reported premenopausal and bilateral disease in her mother, whereas three patients and five controls reported these characteristics in one of their sisters. The correlation between age at diagnosis in familial patients and their mothers or sisters with breast cancer was low -0.38 and 0.29, respectively - and there was no correlation with respect to the occurrence of bilateral disease within the families. (Author abstract) (23 Refs)

24. A PROSPECTIVE COHORT STUDY OF ORAL CONTRACEPTIVES AND BREAST CANCER.

Trapido EJ
Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115
JNCI; 67(5):1011-1015 1981

In 1970 a questionnaire was sent to 97,300 married women aged 25-50 yr residing in eastern Massachusetts. Information was requested on use of oral contraceptives (OC), education, and gyn ecologic and reproductive histories. Subsequent questionnaires were sent in 1973 and 1979 to a subset of the original cohort (37,000) to obtain recent information. Surveillance of 34 hospitals disclosed 622 cases of breast cancer among respondents diagnosed in a 6-1/2 yr period. The rate ratio of breast cancer associated with any use of OC was 0.84 (95% confidence limits: 0.7, 1.1). Although certain subgroups of users experienced significantly lower rates of hospitalization for breast cancer than did nonusers (including users aged 25-29, those for whom less than or equal to 5 yr had passed since first use, women with ages at birth of first child either before 25 or after 30, and women who first used OC after the birth of the first child), the risk of breast cancer was not consistently lower among users of OC. Among nulliparous women, the rate ratio associated with use of OC was 2.1 (0.9, 5.0). (Author abstract) (20 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

25. LOCALIZATION OF MAMMARY TUMORS IN VIVO WITH 131I-LABELED FAB FRAGMENTS OF ANTIBODIES AGAINST MOUSE MAMMARY EPITHELIAL (MME) ANTIGENS.

Wilbanks T, Peterson JA, Miller S, Kaufman L, Ortendahl D, Ceriani RL

(c/o Peterson) Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, 51st and Grove St., Oakland, CA, 94609

Cancer; 48(8):1768-1775 1981

The Fab fragments of antibodies against cell-type-specific surface antigens of mouse mammary epithelial cells (MME-antigens) were used to localize mammary tumors successfully. The radioiodine-labeled anti-MME (Fab) was injected into mice carrying simulated mammary metastases, and after 24 hr the amounts of label per gram of excised tissue was several times greater in the tumor than in liver, brain, lung, or muscle. Kidney showed considerable accumulation of label but this appeared to be nonspecific. Kinetic studies revealed a rapid elimination of labeled Fab in the urine with only 1% of the injected dose remaining in the entire blood pool after 24 hr. With a high-purity germanium camera, mammary tumors were clearly located by the 131I-labeled anti-MME (Fab), and normalization to 99mTc-pertechnetate distribution in the animal increased the specificity. The density of 131I-label was fourfold greater over the mammary tumor than over comparable areas of the mouse. No accumulation of 131I-anti-MME (Fab) was observed in nonmammary tumors nor in mammary tumors when labeled nonspecific Fab was used. An analogous system using an anti-human mammary epithelial antiserum is being developed for localization of breast metastases in humans. (Author abstract) (40 Refs)

26. THE EFFECTS OF IONIZING RADIATION AND OESTROGEN TREATMENT ON THE STEROID-RECEPTOR CONCENTRATIONS IN EXPERIMENTAL MAMMARY CARCINOMA.

Janssens JP, Wittevrongel C, Van Dam J, Goddeeris P, Lauwerijns JM, De Loecker M
Dept. Biochemistry, Faculty Medicine, Univ. Louvain, B-3000 Leuven, Belgium
Biochem Soc Trans; 9(1):95-96 1981

Mammary carcinoma was induced in Sprague-Dawley rats by intragastric injection of 7,12-dimethylbenz[a]anthracene. Tumors appeared after 3 mo. Some rats were irradiated with 20 Gray from a cobalt teletherapy source. Some were treated for three days by sc injection of 5 ug 17beta-estradiol (EDB). Controls remained untreated. Steroid receptor concentrations were determined 40 hr after final hormone treatment or up to 65 days after irradiation. Tumor regression to 25% of pretreatment size occurred during the first 30 days after irradiation. Renewed growth followed, reaching 90% of the pretreatment size by 65 days. EDB-receptor concentrations fell from 2.56 femtomoles/mg (fm/mg) to 1.09 fm/mg during the first 30 days. They remained at the low level during tumor regrowth. Progesterone-receptor levels fell from a control level of 7.39 fm/mg to 1.83 fm/mg during tumor regression and increased during tumor regrowth to 2.36 fm/mg at 65 days. EDB treatment at 65 days restored progesterone-receptor levels to normal control values. EDB-receptor concentrations were not affected by EDB treatment. Evidently the EDB-receptor system, which is necessary for the stimulation of the progesterone-receptor system, remains intact and active after irradiation, although the concentration of receptors is reduced. Interpretation of receptor concentrations measured during endocrine and radiation therapy should be made as a function of these factors. (9 Refs)

27. AN ANTIESTROGENIC ACTION OF ANDROGENS IN HUMAN BREAST CANCER CELLS.

MacIndoe JH, Etre LA
Dept. Medicine, 3E-17, Veterans Admin. Medical Center, Iowa City, IA, 52240
J Clin Endocrinol Metab; 53(4):836-842 1981

We have recently observed that androgens prevent the estrogen-dependent augmentation of cytoplasmic progesterone receptor (PRc) in MCF-7 human breast cancer cells and now report the results of studies that further characterize this new example of sex steroid antagonism. Using a single saturating dose assay to monitor changes in MCF-7 PRc concentration, we have observed that androgens are capable of inhibiting both the estrogenic induction and the ongoing stimulation of PRc synthesis, but have no apparent effect upon basal concentrations of this receptor. Both testosterone and dihydrotestosterone (DHT) demonstrate similar degrees of antiestrogenic activity at concentrations between 10(-10)-10(-8) M. Furthermore, a 10(-8)-M concentration of either androgen completely inhibits the stimulation of PRc synthesis by 10(-11)-10(-8) M 17beta-estradiol (E2). This inhibitory effect is maintained during the continued presence of either testosterone or DHT, but rapidly disappears after the withdrawal of androgen from the culture medium. The specific nuclear binding of 17beta-[3H]estradiol over time appears to be similar in cultures incubated in the presence and absence of 10(-8) M DHT. This observation suggests that androgens do not inhibit estrogen action by interfering with the formation, activation, nuclear binding, or nuclear processing of estrogen-receptor complexes. The estrogenic stimulation of PRc is not diminished by the 5beta-epimer of DHT, and the inhibitory activity of DHT itself is blocked by several different antiandrogens. These findings provide substantial support for the concept that the antiestrogenic effect of androgens is mediated by an androgen receptor mechanism. These results may provide new insights into the clinically apparent antagonistic effects of estrogens and androgens upon both normal and malignant human breast tissues. (Author abstract) (21 Refs)

28. DIFFERENT EFFECTS OF OESTRADIOL, OESTRIOL, OESTETROL AND OF OESTRONE ON HUMAN BREAST CANCER CELLS (MCF-7) IN LONG TERM TISSUE CULTURE.

Jozan S, Kreitmann B, Bayard F
(c/o Bayard) Dept. Endocrinology, INSERM U 168, CHU Rangeil Universite Paul Sabatier, Toulouse 31054, France
Acta Endocrinol (Copenh); 98(1):73-80 1981

The effects of estradiol (Oe2), estrone (Oe1), estriol (Oe3), estetrol (Oe4) on the induction of the progesterone receptor (PgR) and growth of MCF-7 cells are compared. All the four estrogens increase cell PgR concentration. Analysis of the dose-response curves shows induction by Oe2 to be 10x and 50x greater than Oe3 and Oe4, respectively. Oe1 and Oe2 are equally effective, even with consideration of metabolic conversion of Oe1 into Oe2. When compared with untreated cells, Oe2, Oe3 and Oe4 do not influence significantly the plating efficiency but all three hormones increase thymidine incorporation of cells in log phase growth. Oe2, Oe3 and Oe4 are able to rescue the growth inhibition induced by antiestrogens. The respective potency compared to Oe2 is again in the range of 10 and 50x lower for Oe3 and Oe4, respectively. On the other hand Oe1 decreases plating efficiency, thymidine incorporation and does not rescue the growth inhibition induced by antiestrogens when the metabolic conversion of Oe1 into Oe2 is prevented. Thus, Oe3 and Oe4 behave like complete Oe2 agonists whereas Oe1 has dissociated effects, agonist on PgR induction and antagonist on cell growth. (Author abstract) (24 Refs)

29. 5-FLUOROURACIL INCORPORATION INTO HUMAN BREAST CARCINOMA RNA CORRELATES WITH CYTOTOXICITY.

Kufe DW, Major PP
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J Biol Chem; 256(19):9802-9805 1981

We demonstrate a highly significant relationship (p less than 0.0001) between the incorporation of 5-fluorouracil in total cellular RNA and loss of clonogenic survival of the human MCF-7 breast carcinoma cell line. The extent of 5-fluorouracil incorporation in RNA is concentration- and time-dependent. Identical results are obtained in experiments employing thymidine to bypass the block of thymidylate synthetase and reverse inhibition of DNA synthesis. These studies suggest that the incorporation of 5-fluorouracil in RNA is the major mechanism of cytotoxic action in this human cell line. (Author abstract) (24 Refs)

30. PROPHYLAXIS OF MAMMARY NEOPLASIA BY SELENIUM SUPPLEMENTATION IN THE INITIATION AND PROMOTION PHASES OF CHEMICAL CARCINOGENESIS.

Ip C
Dept. Breast Surgery, Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 41(11,part1):4386-4390 1981

The present study was designed to determine the chemopreventive effect of dietary selenium supplementation in the initiation or promotion phase of 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in rats fed a high-fat diet. Control animals received 0.1 ppm of selenium (as sodium selenite), while experimental groups were supplemented with 5 ppm of selenium for various periods of time:-2 to +24,-2 to +2, +2 to +24, +2 to +12, +12 to +24, and-2 to +12. The time of 7,12-dimethylbenz[a]anthracene administration (50 days of age) was taken as Time 0, minus and plus signs represent the time in wk before and after 7,12-dimethylbenz[a]anthracene administration, respectively. The following conclusions were drawn from the results: (a) selenium can inhibit both the initiation and promotion phases of carcinogenesis; (b) a continuous intake of selenium is necessary to achieve max inhibition of tumorigenesis; (c) the inhibitory effect of selenium in the early promotion phase is probably reversible; and (d) the efficacy of selenium is attenuated when it is given long after carcinogenic injury. In addition, the present investigation also assessed the effectiveness of selenium in inhibiting the reappearance of mammary tumors that had regressed after ovariectomy. By supplementing tumor-bearing animals with 5 ppm of selenium in the diet immediately after endocrine ablation, it was found that tumors reappeared at a slower rate compared to the controls. The data suggested that selenium is not only effective in chemoprevention but can also be used as an adjuvant chemotherapeutic agent. (Author abstract) (35 Refs)

31. CLONAL PROLIFERATION OF CULTURED NONMALIGNANT AND MALIGNANT HUMAN BREAST EPITHELIA.

Smith HS, Lan S, Ceriani R, Hackett AJ, Stampfer MR
Dept. Surgery, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Cancer Res; 41(11,part1):4637-4643 1981

We have developed a method for clonal growth of human mammary epithelial cells of both nonmalignant and malignant origin. Plating efficiencies of 1 to 50% were obtained by seeding second-passage mammary epithelial cells on fibroblast feeder layers in an enriched medium composed of various hormones and growth factors, as well as conditioned media from three specific human cell lines. Single mammary epithelial cells seeded sparsely onto the fibroblasts underwent at least eight population doublings to form large, readily visible colonies. Optimal colony formation required both feeder cells and the enriched medium. Epithelial colonies containing at least 16 cells were visible 5 days postseeding, and these colonies continued to grow progressively. Plating efficiency and colony size were similar on UV-irradiated or nonirradiated fibroblasts. The number of colonies formed was proportional to the number of epithelial cells plated. The colonies were identified as epithelial by the presence of human mammary epithelial antigens. (Author abstract) (31 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abou-Issa H. 5
Adami HO 23
Adams J 12
Adil MA 13
Avila C 15
Baroncelli C 16
Bayard F 28
Berg O 1
Bezwoda W 14
Blumenschein GR 17
Bodey GP 17
Bono A 8
Bostofte E 1
Bothwell T 14
Botnick LE 19
Boulter PS 2
Bukowski R 9
Buzdar AU 17
Carrion P 15
Carton FX 3
Casadei BM 16
Ceriani R 31
Ceriani RL 25
Chamness GC 11
Curto M 15
Daidone MG 6
De Carli A 8
De Loecker M 26
De Moor N 14
Derman D 14
Deutsch M 20
Di Pietro S 8
DiStefano A 17
Dieval M 3
Dinner MI 21
Ducrocq C 3
Edwards DP 11
Elliot JB 5
Etre LA 27
Fisher B 20
Fisher ER 20
Foecking MK 5
Galante E 8
Gallus G 8
Garcia M 12
Gentili C 6
Goddeeris P 26
Goldstein MA 19
Greenstreet R 9
Groppe C 9
Grumbach Y 3
Guzzon G 8
Hackett AJ 31
Hansen J 23
Harris JR 19
Hart RD 18
Hellman S 19
Herzog AG 19
Holland JF 18
Hortobagyi GN 17
Ignesti C 16
Innocenti V 16
Ip C 30
Janssens JP 26
Jensen HM 7
Jozan S 28
Jung B 23
Kaufman L 25
Kreitmann B 28
Kufe DW 29
Labandter HP 21
Lan S 31
Lauwerijns JM 26
Lenzi L 16
Levene MB 19
Levin J 14
Livolsi VA 4
MacIndoe JH 27
MacPhil P 14
Major PP 29
Massieu C 15
Matthews RH 5
Mauri M 8
McDonald MW 10
McGuire WL 11
Mercer WD 11
Merino MJ 4
Merson M 8
Miller S 25
Minton JP 5
Mortimer J 9
Neely CL 10
Niell HB 10
Ortendahl D 25
Palmieri GM 10
Participating N 20
Pennisi VR 22
Perloff M 18
Peterson JA 25
Price JL 2
Redmond C 20
Reimer R 9
Rimsten A 23
Rochefort H 12
Roseman JM 5
Salner AL 19
Salvadori D 16
Serup J 1
Sheth AR 13
Sheth NA 13
Silvestrini R 6
Smith HS 31
Stampfer MR 31
Suraiya JN 13
Thomas BA 2
Trapido EJ 24
Van Dam J 26
Wilbanks T 25
Wittevrongel C 26
Wolmark N 20
Yap HY 17

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS) 1
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS 2-8
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS 9-19
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS 20-24
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY) 25-36
- SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS) 37
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY 38-41
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY) 42-47

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BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. CLINICAL APPLICATION OF A NEW ULTRASONIC MASS-SCREENING SYSTEM FOR DETECTION OF BREAST CANCER.

Takehara Y, Kashida R, Matsukawa M, Hisada Y, Iinuma K, Takamizawa K
Kanto Central Hosp., Tokyo, Japan
Excerpta Med Int Congr Ser; 539:398-403 1981

The subject bends forward over a specially designed tank so that both breasts are immersed in de-gassed water at 37 C. A vinyl membrane 1-2 cm below the water surface controls in some degree the distance between breast and transducer. In the tank bottom is an electronic linear array transducer (200 x 15 mm) which is pivoted forward to the breasts and moves mechanically in a 180 degree arc, taking about 2 min for a scan. The ultrasonic beam is electronically condensed. Recording, formerly done by VTR, is now done with a video-disc recorder. From April 17, 1979 to June 30, 1980, 983 cases were studied with this equipment: 658 breasts were normal, 314 showed various benign, and 11 malignant tumors. The high rate of tumor detection is partly due to the fact that some subjects were from the outpatient clinic. The equipment has proved satisfactory as to scanning area and time required for examination, but has yet to be evaluated in relation to tumors less than 5 mm. Specifications are presented and some technical difficulties of the equipment are discussed. (7 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. ULTRASOUND MAMMOGRAPHY: DIFFERENTIAL DIAGNOSIS OF BREAST CANCER - A COMPARISON WITH OTHER METHODS (MEETING ABSTRACT).

Hackeloer BJ, Eulenburg R, Huneke B, Duda V, Lauth G, Buchholz R
No affiliation given
Excerpta Med Int Congr Ser; 547:118 1981

One hundred and fifty carcinomata of the breast were examined by ultrasound mammography and compared to (1) clinical examination, (2) thermography, (3) x-ray mammography, (4) cytology, and (5) operative findings and histology. While x-ray mammography was superior in the detection of the total number of carcinomata there were some carcinomata demonstrable by ultrasound and not detectable by x-ray. The smallest carcinoma we were able to demonstrate was 3x4 mm in size. These results indicate that ultrasound cannot be used as a true screening procedure. But there is a significant difference in the demonstration of different tumor types, eg the scirrhous carcinoma was easy to recognize but the solid carcinoma was not. We tried to give a differential diagnosis for different types of cancer using a full description of the typical cancer tissue texture (christmas-tree sign) and indirect, functional signs like 'lateral and middle shadowing'. Ultrasound mammography can be regarded as a new ancillary aid in the differential diagnosis of a malignancy and should be used because of its noninvasiveness as a method of first choice. (no Refs)

3. ROLE OF BONE SCANS IN THE INITIAL ASSESSMENT OF OPERABLE PATIENTS WITH BREAST CARCINOMA.

Strender LE, Lagergren C, Wallgren A, Liljevall S
Radiumhemmet, Karolinska Sjukhuset, S-104 01 Stockholm, Sweden
Acta Radiol Oncol Radiat Phys Biol; 20(3):187-191 1981

The yield and the prognostic significance of initially performed bone scintigraphy in 387 patients with operable mammary carcinoma are reported. The mean follow-up time was 52 mo. In 12 patients (3.1%) the scintigraphy was considered to indicate bone metastases but it only 3 of these bone metastases later developed. The low information obtained has resulted in exclusion of bone scintigraphy in the initial assessment of clinically operable patients with mammary carcinoma. (Author abstract) (19 Refs)

4. ABNORMAL NIPPLE ASPIRATE CYTOLOGY AND PROLIFERATIVE CHANGES IN BENIGN BREAST DISEASE (MEETING ABSTRACT).

King EB, Chew K, Barrett DL, Ernster V, Petrakis NL
University of California School of Medicine, San Francisco, CA
Acta Cytol (Baltimore); 25(4):450 1981

Abnormal nipple aspirate cytology is found with increased frequency in women with breast cancer risk factors, such as benign breast disease. The purpose of this report is to describe an anatomic basis that we have found for the significance of abnormal cells in these women. Nipple secretions and subsequent benign breast biopsies from 232 women were examined. Duct epithelial cells were classified as normal or as cells representing a duct epithelial proliferative process. The latter constituted a continuum of increasing abnormality, to which the terms hyperplasia, atypical hyperplasia and dysplasia were applied. The duct epithelium in the breast tissue from biopsy was reviewed independently and classified using the same terminology used for the aspirate samples. We found a significant association between ductal atypia in the nipple aspirate and breast tissue specimens: women with abnormal cytology were more likely than women with benign cellular findings to have a histologic diagnosis of proliferative disease with atypia. These results confirm the anatomic basis of abnormal cytology in our study of breast cancer risk factors, although the cytologic results were not sufficiently predictive to be used for diagnostic purposes. (no Refs)

5. COMPLICATIONS IN NEEDLE ASPIRATION CYTOLOGY OF THE BREAST: A CONSIDERATION COMPARING MEDIUM-GAUGE AND FINE-GAUGE NEEDLE ASPIRATION (MEETING ABSTRACT).

Betsill WL, Walker AN
Department of Pathology, Medical University of South Carolina, Charleston, SC
Acta Cytol (Baltimore); 25(4):444 1981

All needle aspirations of the breast from the University of Virginia Medical Center (1978-79) were evaluated regarding morbid complications of the needle aspiration technique. Morbidity was directly related to the outside diameter of the needles utilized. Generally, needle aspiration of the breast was performed by (1) the surgeon using 18-guage needles (1.27 mm outside diameter) or (2) the pathologist using 22-or 23-guage needles (outside diameter 0.64 to 0.72 mm). Infarction of two benign breast lesions occurred due to the mechanical disruption of vascularity by needle trauma. In both instances, an 18-guage needle was used (approx 10% complication rate). This contrasts with the 0 complication rate utilizing the fine needle aspiration technique (22-or 23-guage needle). The trauma induced by the medium-gauge needle resulted in pain, swelling and intralesional hemorrhage necessitating immediate surgical excision in the two cases. The results of the needle aspiration attempts utilizing medium- and fine-gauge needles are compared with respect to diagnostic accuracy, degree of cellularity and percentage of cases necessitating subsequent needle aspirations and/or excisional biopsy to confirm the cytologic diagnosis. The effects of trauma are evaluated in surgically resected specimens. We could define no conclusive evidence to support the use of the medium-guage needle (18 guage) and strongly suggest that needle aspiration attempts be performed with the fine needle (22 or 23 gauge). (no Refs)

6. PROGNOSIS IN STAGE II (T1N1M0) BREAST CANCER.

Rosen PP, Saigo PE, Braun DW, Weathers E, Kinne DW
Memorial Hosp., 1275 York Ave., New York, NY, 10021
Ann Surg; 194(5):576-584 1981

As part of a detailed study of prognostic factors in breast cancer, we have analyzed the 10 yr survival rates of 524 patients with primary invasive carcinomas 2.0 cm or less in diameter (T1). This report describes the subset of 142 patients (27%) who had metastases only in axillary lymph nodes (T1N1M0). All the patients were treated initially by at least a modified radical mastectomy. Factors associated with a significantly poorer prognosis were: axillary lymph node metastases suspected on clinical examination; perimenopausal menstrual status at diagnosis; tumor larger than 1.0 cm; prominent lymphoid reaction; infiltrating duct or lobular rather than medullary, colloid and tubular carcinoma; and blood vessel invasion. When compared with those patients with negative nodes (T1N0M0), the patients with one or more lymph node metastases had a significantly poorer prognosis. Generally, survival rates tended to diminish as the number of involved lymph nodes increased. In this respect, comparison of patients with one-three and four or more nodal metastases provided a significant discrimination of prognostic groups in the entire series. However, for patients with disease limited to Level I, the same discrimination was obtained comparing those with one-two and three or more positive nodes. In the subset with a single lymph node metastasis, the size of the metastasis (micro or less than or equal to 2 mm vs macro or greater than 2 mm) was not significantly related to prognosis. Lymph node metastases were significantly less frequent among tumors smaller than 1 cm and special tumor types (medullary, colloid, lobular and tubular). However, no factor proved to be a reliable predictor of the presence of axillary metastases for the single largest group consisting of patients with infiltrating duct carcinoma 1-2 cm in diameter. (Author abstract) (24 Refs)

7. AXILLARY MICRO- AND MACROMETASTASES IN BREAST CANCER: PROGNOSTIC SIGNIFICANCE OF TUMOR SIZE.

Rosen PP, Saigo PE, Braun DW, Weathers E, Fracchia AA, Kinne DW
Memorial Hosp., 1275 York Ave., New York, NY, 10021
Ann Surg; 194(5):585-591 1981

Recurrence and survival data at 10 yr were examined for 147 women with single axillary node metastases found in a modified radical or standard radical mastectomy. The cases were identified through a review of all patients with primary operable breast cancer treated at Memorial Hospital for 1964 to 1970. The patients were stratified into groups according to size of the primary tumor and of the metastatic deposit (micro less than or equal to 2 mm; macro greater than 2 mm) as well as level of the positive node. In the entire series, there was a significantly poorer prognosis among those patients with single macrometastases (30/77 patients; 39% recurrence rate) when compared with those having macrometastases (17/70 patients: 24% recurrence rate). A major prognostic difference emerged after stratification by tumor size. Within the first 6 yr of the follow-up period, T1 patients with negative nodes and those with single micrometastases had similar survival curves, significantly better than those with macrometastases. However, at 12 yr, the survival rate of those patients with either a micro- or macrometastasis was nearly identical, and significantly worse than for those patients with negative lymph nodes. On the other hand, among women with primary tumors 2.1-5.0 cm (T2), patients with negative lymph nodes or single micrometastases had survival curves that did not differ significantly throughout the course of the follow-up period. Both had an outcome significantly better than observed for patients with macrometastases. These findings have important implications for our understanding of the clinical behavior of breast cancer and for the stratification of patients entered into randomized treatment trials. (Author abstract) (10 Refs)

8. BASEMENT MEMBRANE CHANGES IN BREAST CANCER DETECTED BY IMMUNOHISTOCHEMICAL STAINING FOR LAMININ.

Albrechtsen R, Nielsen M, Wewer U, Engvall E, Ruoslahti E

Univ. Inst. Pathological Anatomy, Frederik V's vej 11, DK-2100 Copenhagen, Denmark

Cancer Res; 41(12):5076-5081 1981

The distribution of the basement membrane glycoprotein laminin was studied by the immunoperoxidase technique in benign and malignant human breast tissue and in axillary lymph nodes from patients with breast cancer. An antiserum prepared against rat laminin was used. The specificity of this antiserum against laminin was studied using the FL cell line of human epithelial-like cells derived from normal amniotic membrane. The antiserum reacted with these cells in immunoper[illegible] staining and precipitated metabolically labeled secreted polypeptides which comigrated with polypeptides with mol wt of 400,000 and 200,000 of rat laminin in sodium dodecyl sulfate:polyacrylamide gel electrophoresis. The neoplastic cells in malignant breast tissues showed strong cytoplasmic staining for laminin, and a positive reaction was also found in lymph node metastases. In some cases in which only micrometastases were present, these cells also stained strongly for laminin. In nonmalignant breast tissues, the epithelial cells of the ducts were positive for laminin, but the staining was weaker than in the carcinomas. Pretreatment of the fixed tissue sections with trypsin markedly enhanced the staining of basement membranes for laminin. In trypsin-treated sections of normal breast tissue and benign lesions, the laminin staining delineated continuous basement membranes. In carcinomas representing the more differentiated types, basement membranes presumably produced by the tumor cells could be revealed by laminin staining, but they were thinner and discontinuous. The poorly differentiated carcinomas lacked organized basement membranes detectable by laminin staining. Our studies suggest that staining for laminin may be a useful adjunct test for detection of micrometastases in lymph nodes. The correlation of disintegration of the laminin-containing basement membranes of tumors with increasingly anaplastic appearance supports the notion that basement membranes may play a role in tumor invasion. (Author abstract) (33 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

9. PROGESTERONE RECEPTORS AS AN INDICATOR OF THE RESPONSE OF POST-MENOPAUSAL ENDOMETRIAL CARCINOMA AND METASTATIC BREAST CANCER TO AN ANTIESTROGEN (MEETING ABSTRACT).

Robel P, Mortel R, Levy C, Namer M, Baulieu EE
Laboratory Hormones, 94270 Bicetre, France
Progesterone and Progestins, International Symposium, May 7-9, 1981, Paris, France Centre National de la Recherche Scientifique; 1981

Estradiol (ER) and progesterone receptor (PR) concentrations were determined in cytoplasmic and nuclear fractions of endometrial cancer specimens taken from 43 post-menopausal women. All tumors except 1 contained variable, often large, amounts of total ER. The total PR concentration was generally low and considered undetectable or insignificant in 10 cases. No significant correlation was found between receptor concentrations and histological grading. Fifteen patients received tamoxifen (Tam) po (40 mg daily for 5 to 7 days, Group 1) and 10 patients ingested 10 mg of Tam 8 and 4 hr prior to a second endometrial sampling (Group 2). In addition to receptors, ornithine-decarboxylase activity (ODC) was also measured before and after Tam treatment. PR concentrations in Group 1 increased significantly but ODC did not. Because Tam may have induced a rapid and transitory increase of enzyme activity, ODC was studied in Group 2 patients. Again no change in the enzyme activity was observed. PR did not vary but nuclear ER increased indicating Tam effectiveness. Available cytoplasmic ER and PR sites were measured in biopsies of skin metastatic nodules removed from 21 post-menopausal women with advanced breast cancer. All patients received 30 mg of Tam daily for 7 days. When present, ER was greatly decreased. No PR change was recorded in cases where ER was less than 20 fmol/mg cytosol protein. Six of the 12 remaining cases showed an increase of PR greater than 100 fmol/mg cytosol protein. We conclude that repeated tumor sampling should be considered whenever possible, allowing an in vivo challenge with Tam to predict hormone responsiveness on the basis of large PR increase. (no Refs)

10. CYTOSOL OESTROGEN AND PROGESTERONE RECEPTORS, NODE STATUS AND EARLY RECURRENCE OF PRIMARY BREAST CANCER (MEETING ABSTRACT).

Howat JM, Harris M, Swindell R, Barnes DM
Christie Hospital, Manchester M20 9BX, England
Br J Cancer; 43(5):718 1981

This is a preliminary report on cytosol estrogen receptors (REc) measured in tumor cytosols from 175 patients treated by modified radical mastectomy in whom there was histological proof of the presence or absence of axillary node involvement. At a median follow-up of 24 mo (range 1-48 mo) the occurrence rate was significantly lower in patients whose tumors were RE+ than in those whose tumors were RE-. There was no difference in the recurrence rates of progesterone receptors (RP)+ and RP- tumors. The overall recurrence rate was significantly higher in node-positive patients regardless of the receptor status none the less a significant improvement in disease-free interval was seen in RE+ patients when node status was taken into account. When analyzed with regard to the degree of node involvement it was only those patients with few nodes (1-3) who benefited by having RE, for they had a significant improvement in the desease-free interval when compared with RE- patients. No significant difference in recurrence rate was seen in node-negative patients, nor in those with more than 4 axillary nodes. (no Refs)

11. STEROID RECEPTORS IN EARLY BREAST CANCER: VALUE IN PROGNOSIS (MEETING ABSTRACT).

Griffiths K, Nicholson RI, Blamey RW, George D
City Hospital, Nottingham, England
Fifth International Symposium of the Journal of Steroid Biochemistry, July 13-15, 1981, Puerta Vallarta, Jalisco, Mexico. Journal of Steroid Biochemistry 80 pp., 1981.

The relationship of prognosis to estradiol-17 receptor (ER) status of primary breast tumors has been studied (a) in 550 patients who presented consecutively to one surgeon and (b) 414 patients dealt with by 15 surgeons. Patients in (a) were staged after a triple-node biopsy according to node involvement, those in (b) by the tumor, node, metastasis (TNM) system. All patients were followed-up witho ut treatment until recurrence. In group (a), 82 patients have had local or regional recurrence, 42 of whom also developed distant metastases. Forty-two developed distant metastases without prior local recurrence. ER status was related to tumor grade, disease free interval and survival. Furthermore ER status, with stage and grade, can be used to select good or bad prognostic groups. The site of metastases, a clinical factor of prognostic significance also related to ER status, ER + tumors tending to recur to bone, ER- to the viscera. In group (b), ER status also related to recurrence and survival, ER+, lymphnode negative (LN-) patients had a good prognosis. Conversely ER-LN+ had a poor prognosis. Of particular interest in the group (b) study, ER-LN- patients could be identified as a high risk group with a survival rate similar to all LN+ patients. (no Refs)

12. OESTROGEN-RECEPTOR STATUS AND SITES OF METASTASIS IN BREAST CANCER.

Campbell FC, Blamey RW, Elston CW, Nicholson RI, Griffiths K, Haybittle JL
Dept. Surgery, City Hosp., Nottingham NG5 1PD, England
Br J Cancer; 44(3):456-459 1981

The estrogen receptor (RE) status of the primary tumor has been assessed in 466 of a consecutive series of 550 patients with primary operable breast cancer. All patients were followed up (without treatment) until the development of recurrence or metastases. Distant metastases have so far occurred in 124 patients and 82 have had symptomatic local or regional recurrence. A significant correlation exists between the RE status of the primary tumor and subsequent patterns of metastasis. Symptomatic metastases to regional lymph nodes are more common with RE- cancers. There is no significant difference in either time of onset or total incidence of distant metastases between patients with RE+ and RE- tumors. Distribution of distant metastases is influenced by RE status: RE+ tumors tend to recur in bone, RE- tumors show affinity for viscera. (Author abstract) (16 Refs)

13. OESTROGEN RECEPTORS AND SURVIVAL IN EARLY BREAST CANCER.

Croton R, Cooke T, Holt S, George WD, Nicolson R, Griffiths K
Dept. Surgery, Royal Liverpool Hosp., Liverpool L69 3BX, England
Br Med J; 283(6302):1289-1291 1981

Estrogen receptor status was related to survival in 414 patients with primary breast cancer. Women with estrogen receptors in their tumors survived significantly longer than those without receptors; this was true for both premenopausal and postmenopausal women and also when the patients were subdivided into those with and without axillary metastases. Patients with axillary metastases and no estrogen receptors in their tumors had the worst prognosis, while women with axillary metastases and estrogen receptors had a death rate similar to that of women with no axillary metastases and no receptors. Patients without estrogen receptors and with no axillary metastases were identified as a high-risk group, and it would seem appropriate to include such patients in future trials of adjuvant therapy in early breast cancer. (Author abstract) (7 Refs)

14. ESTROGEN RECEPTOR STATUS AND DEATH FROM BREAST CANCER: PRELIMINARY REPORT (MEETING ABSTRACT).

Critselis AN, Carson EJ, Autuoro LM, Brockmeyer D, McDowell K, Degenshein GA
Department of Surgery, Maimonides Medical Center State University of New York, Downstate Medical, Center Brooklyn, NY
Eur Surg Res; 13(1):30 1981

The value of estrogen and progesterone receptor (ER, PgR) analysis of the primary tumor for the establishment of the prognosis of breast cancer patients is still under investigation. The ER status of patients with breast cancer, who succumbed to their disease, was investigated and correlated with that of surviving patients. One hundred eighty-nine patients with stage I or II breast cancer were followed up for a minimum of 12 mo postradical or modified radical mastectomy. Tumor specimens from all patients were subjected to ER and/or PgR analysis, using the dextran-coated, charcoal-binding method. Age, menopausal status and tumor, node, metastasis staging were recorded for each patient. Progressive disease was confirmed by a radiological, laboratory and/or histological work-up. To date, 26 patients have died due to carcinomatosis and 163 patients are disease-free. The data indicate that a direct correlation exists between and ER- status and mortality. Specifically, the ER+/ER-ratio was only 0.62 for the group of patients who died, as compared to 1.40 for the disease-free patients. The later value (1.40) was identical to that obtained when the entire group of 518 tumor samples, from patients all all stages of disease, assayed in our laboratory during the past 5 yr, was considered as a whole. These preliminary data indicate a strong association between ER status and prognosis in breast cancer patients. (no Refs)

15. CONJUGATED ESTROGENS AND BREAST CANCER RISK IN WOMEN.

Hoover R, Glass A, Finkle WD, Azevedo D, Milne K
Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(4):815-820 1981

The relationship between conjugated estrogen(s) (CE) and breast cancer was investigated by the examination of the records of 345 women with newly diagnosed breast cancer and 611 healthy controls belonging to a prepaid health plan. Use of CE was associated with a 40% elevation in risk [relative risk (RR) = 1.4; 95% confidence interval = 1.0-2.0]. The RR was 1.3 for menopausal women with intact ovaries and 1.5 for those with ovaries removed. There was statistically significant evidence of a dose-response relationship with the three measures of dose evaluated. RR's rose to about twofold for women with 10 or more CE prescriptions noted in their charts, for those with 5 yr or more between their first and past prescription, and for those with a usual daily dose of 1.25 mg or more. The RR associated with having ever used CE and with long-term use was highest among those women with a family history of breast cancer. These data support the hypothesis that long-term use of CE is associated with increased breast cancer risk. (Author abstract) (41 Refs)

16. STEROID METABOLISM AND OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

Miller WR, Hawkins RA, Forrest AP
Dept. Clinical Surgery, Univ. Edinburgh, Edinburgh, Scotland
Eur J Cancer Clin Oncol; 17(8):913-917 1981

Metabolism of 7alpha[3H] testosterone and estrogen receptor activity have been measured in 54 human breast cancers. All tumors converted testosterone to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol, but unequivocal evidence for production of estradiol was obtained in only 29 of the tumors. Thirty-seven tumors were classified as estrogen receptor 'positive' containing levels in excess of 5 fmol/mg cytosol protein. Although mean conversions to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol were all higher in estrogen receptor negative tumors as compared with receptor positive group, the differences did not reach statistical significance. There was, however, a significant trend for estradiol synthesis to be associated with estrogen receptor positive tumors (p less than 0.025). All tumors with very high level of receptors converted testosterone to estradiol. (Author abstract) (21 Refs)

17. STUDIES ON SIALYLTRANSFERASE ISOENZYMES IN PLASMA OF PATIENTS WITH BREAST CANCER.

Kessel DH, Chou TH, Coombes RC
Dept. Oncology, Harper Hosp., Detroit, MI, 48201
Eur J Cancer Clin Oncol; 17(9):1035-1040 1981

An elevated level of sialyltransferase was often found in plasma of patients with breast cancer, but the extent of this elevation was highly variable, as was the enzyme level in plasma of normal donors. Electrofocusing studies indicated the presence of sialyltransferases, focusing at pH 5.2 and 5.6, in all plasmas examined. Elevated enzyme activity in plasma of normal donors was associated with appearance of an 'inflammatory response' isoenzyme with pI = 7.5. In plasma of the individuals with untreated primary or recurrent breast cancer, we found a new sialyltransferase isoenzyme with pI = 4.7. This isoenzyme was not detected in plasma of patients with benign breast disease. (Author abstract) (19 Refs)

18. SEQUENTIAL GALACTOSYLTRANSFERASE AND CARCINOEMBRYONIC ANTIGEN LEVELS IN ADVANCED BREAST CARCINOMA.

Paone JF, Baker RR, Waalkes TP, Shaper JH
Dept. Surgery, Johns Hopkins Hosp., Baltimore, MD, 21205
J Surg Res; 31(4):269-273 1981

UDP-galactosyltransferase (GT), an enzyme that functions in the biosynthesis of glycoproteins, has recently been found to be a sensitive biologic tumor marker. In the present study, sequential GT levels were compared to simultaneous CEA determinations to establish which biomarker more accurately reflects changes in tumor activity in patients receiving therapy for advanced breast carcinoma. Serum levels of GT and CEA were measured each mo in 38 patients undergoing combination chemotherapy for metastatic breast carcinoma. The results were correlated with the objective responses observed to chemotherapy during this period. Prior to the institution of chemotherapy, significant serum GT elevations were observed in 84.2% (32/38) of the patients, while 55.3% (21/38) had elevations in levels of CEA. During therapy 71.4% (10/14) and 50% (7/14) of the GT and CEA levels, respectively, decreased in patients who had an objective response to therapy. In the patients whose disease progressed on therapy, 75% (18/24) had significant increases in GT levels during this interval, while 41.6% (10/24) had increases in CEA (p less than 0.01). Furthermore, in 11 patients (29.5%) serum GT alterations correctly reflected changes in tumor activity, while CEA levels remain static. These data indicate that GT is more sensitive than CEA as a marker for breast carcinoma and suggest that GT may be clinically useful in the management of patients with metastatic breast disease. (Author abstract) (21 Refs)

19. GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY IN HUMAN BREAST CANCER: LACK OF ASSOCIATION WITH OESTROGEN RECEPTOR CONTENT.

Poulsen HS, Frederiksen P
Inst. Cancer Res., Radiumstationen, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark
Acta Pathol Microbiol Scand [A]; 89(4):263-270 1981

The correlation between glucose-6-phosphate dehydrogenase activity and different tumor characteristics was investigated in human breast cancer tissue. The enzyme activity was measured by a histochemical method and the estrogen receptor content by a dextran-coated charcoal assay. The proliferative activity of the tumors correlated positively with the glucose-6-phosphate dehydrogenase activity. No correlation was found between enzyme activity and tumor type and menopausal status, age, TNM-class nor estrogen receptor content. Based on this investigation it is concluded that the activity of glucose-6-phosphate dehydrogenase reflects the proliferative status of the tumor but not the hormone dependency of the tumor. (Author abstract) (24 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

20. COMBINATION CHEMOIMMUNOTHERAPY WITH FAC-BCG FOR METASTATIC BREAST CANCER: THE IMPACT OF CMF MAINTENANCE CHEMOTHERAPY.

Hortobagyi GN, Blumenschein GR, Buzdar AU, Yap HY, Schell FC, Barnes BC, Burgess MA
Medical Breast Service, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
J Surg Oncol; 18(2):163-172 1981

In an attempt to prolong the durations of remission and survival of patients with advanced breast cancer treated with the FAC(5-Fluorouracil, Adriamycin, cyclophosphamide)-BCG protocol, we modified the CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) maintenance combination by increasing the dose of all three drugs and administering them iv. Eighty-five evaluable patients treated with this new regimen were compared with a recent historical control group of 105 evaluable patients treated with FAC-BCG and a lower-dose, oral CMF maintenance program. The overall (70% and 76%) and complete (16% and 19%) response rates were identical in these two groups. The median times to progression for all patients entered were similar too (13 mo for both groups). The durations of response were 17 mo (PO-CMF) and 14 mo (IV-CMF), not significantly different ($p = 0.16$). The durations of survival of the two treated groups were also very similar. After the administration of intensive FAC induction therapy, a high-dose, iv CMF maintenance program appears no better than a low-dose oral regimen. Other drug combinations consisting entirely of drugs not used in the induction regimen might be better choices for maintenance treatment. (Author abstract) (16 Refs)

21. VALUE OF THE TISSUE POLYPEPTIDE ANTIGEN (TPA) DETERMINATION IN MAMMARY CARCINOMA (MEETING ABSTRACT).

Doepp M, Laubenberger Th
No affilation given
Eur J Nucl Med; 6:49 1981

The determination of carcinoembryonic antigen is well established in the staging of mammary carcinoma (MC). The new oncofetal antigen TPA is considered to have a higher positive incidence than carcinoembryonic antigen. We investigated 87 women with MC who were diagnosed by histology, lung x-ray, liver scan, whole body bone scan, and liver ultrasound. Five groups were formed: 1) pre-op without metastases (M), 2) pre-op with M. 3) post-op without M, 4) post-op with M, 5) post-op with uncertain M. Results: TPA concentrations of the 5 groups: 1) 127 +/-32, 2) 231 +/-112, 3) 56 +/-19, 4) 214 +/- 97, 5) 83 +/-23. Upper limit of normals (3) is 90, as found in previous studies. The correlation between the number of M and the TPA is positive: R equals + .56, high significance. Two cases of (4) had to be excluded because of excessive TPA of 1000 U/L. They had additionally colon cancer some yr before, presumably with M from that origin. Group (5) could be subdivided in 3 cases with strong and 4 cases with light suspicion by means of TPA. Without group (5), the sensitivity of the TPA resulted in 65%, the specificity in 93%, and the predictive accuracy in 100%. Thus, an elevated TPA proves malignant growth, a normal value does not exclude it. (no Refs)

22. ANTI-I ACTIVE COLD AGGLUTININS AND B-CELL LYMPHOCYTOTOXINS IN BREAST CANCER SERA (MEETING ABSTRACT).

Anderson B, Dube VE, Iwaki Y, Terasaki P
Department of Biochemistry, Northwestern University Medical School, Chicago, IL
Oncodev Biol Med; AbstractsBook,1:P20 1981

The I, i antigens are a family of carbohydrate sequences which are precursors to the A,B,O blood group substances, that are expressed on adult and fetal epithelial and lymphoid tissues, and for which naturally occurring anti-I IgM class cold reactive antibodies exist. In this study the serum cytotoxic activity towards B lymphocytes was determined for 98 individuals with breast carcinoma and related to the anti-I cold agglutinin levels. Significantly increased frequencies of B-cell cytotoxins were found in the cancer sera in comparison to a control group. Lymphocytotoxic activities in the cancer sera were also associated with significant increases in RBC cold agglutinin levels. Serum IgM concentrations were also higher in patients with B-lymphocytotoxins compared to patients and controls without lymphocytotoxins. No significant changes in the frequency of lymphocytotoxicity were found for the individual stages of cancer compared to each other, nor for the various histological types of breast malignancy. These anti-I auto-antibodies, in a manner similar to previously characterized anti-

IgM lymphocytotoxins, may affect B cell functions or B-T lymphocyte interactions, possibly resulting in a tumor-enhancing effect. (no Refs)

23. URINARY CANCER-RELATED PROTEIN, EDC1, AS IMMUNODIAGNOSTIC MARKER IN BREAST CANCER (MEETING ABSTRACT).

Chawla RK, Miller FW, Lawson DH, Richmond A, Rudman D
Department of Medicine, Emory University, Atlanta, GA
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

A novel glycoprotein labeled EDC1, mol wt 27.5 K, was isolated originally from the urine of a leukemic patient ED. This protein inhibited trypsin, chymotrypsin and human plasmin and was immunologically related to a normal plasma protein inter-alpha trypsin inhibitor (IATI) mol wt 160 K. By using a specific and sensitive radioimmunoassay for EDC1, urinary levels of this protein were measured in i) normal healthy women, ii) women with metastatic breast cancer, iii) patients with non-neoplastic diseases, and iv) preoperative patients with localized breast mass. The urinary excretion of EDC1 (mg/g creatinine) was classified in four ranges; i) normal less than 15 mg; ii) light 15-30 mg; iii) intermediate 31-45 mg; and iv) heavy greater than 45 mg. The av +/- SEM values were as follows: 8.0+/-2.2 for normal women and 98.6+/-11 for metastatic breast cancer patients. In the 26 preoperative patients, subsequently shown to have benign les ions, the EDC1 excretion was 21.5+/-3.4; 24 of these patients were in the normal to light and 2 were in the intermediate range of excretion. In the other preoperative subgroup (27 patients subsequently shown to have malignant lesions), the av EDC1 excretion was 43.1+/-7.6 mg with 8 normal, 5 light, 4 intermediate and 10 heavy excretors. A direct correlation existed between the number of nodes and the level of EDC1. Further analysis showed a negative correlation between plasma levels of IATI and urinary EDC1 levels in metastatic breast cancer patients. In normal plasma, the immunoreactive (IR)-IATI material was found to exist in three molecular forms viz with mol wt 160 K, 110 K and 60 K. In patients with metastatic breast cancer, who were heavy excretors of EDC1, the IR-IATI corresponding to mol wt 60 K was absent and their total IR-IATI was about 2/3 of that in normals. When normal plasma was incubated with trypsin or with human plasmin for 4 hr, the IR-IATI shifted to the mol wt 30 K region. These data suggest tht in cancer urinary EDC1 may arise as a result of selective degradation of IATI by cancer-associated proteolysis and that IATI may be one of the primary inhibitors for this enzymatic activity. (no Refs)

24. THE SIGNIFICANCE OF IMMUNOLOGICAL INVESTIGATIONS DURING RADIOTHERAPY FOR BREAST CANCER.

Boller B, Karcher KH
(c/o Karcher) Universitatsklinik fur Strahlentherapie und Strahlenbiologie, Alser Strasse 4, A-1090 Wien, Austria
Wien Klin Wochenschr; 93(17):547-551 1981

Immune response was measured in a group of 50 patients with carcinoma of the breast. Factors to be determined included (1) the influence of the tumor on immmunocompetence (IC), (2) the influence of removal of visible tumor on IC, (3) the influence of local irradiation on IC, (4) the influence of other therapeutic measures on IC, (5) indication of tumor recurrence or progression by IC parameters, and (6) indication of the course of disease by changes in IC during therapy. Parameters measured included IgA, IgG, IgM, IgE, lymphocyte migration, lymphocyte membrane fluorescence, T cell rosette formation, granulocyte phagocytosis, and reactions to skin tests. At the time of study 12 patients had died, 20 showed metastases, and 6 showed recurrence of tumor. Results were compared with results for patients with benign tumors and for healthy individuals. No useful clinical methods could be developed for early diagnosis, prognosis, or measurement of disease progress based on immune response. (23 Refs) (In GER)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

25. PRELIMINARY OBSERVATIONS OF THE EFFECTS ON BREAST ADENOCARCINOMA OF PLASMA PERFUSED OVER IMMOBILIZED PROTEIN A.

Terman DS, Young JB, Shearer WT, Ayus C, Lehane C, Mattioli C, Espada R, Howell JF, Yamamoto T, Zaleski HI, Miller L, Frommer P, Feldman L, Henry JF, Tillquist R, Cook G, Daskal Y
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
N Engl J Med; 305(20):1195-1200 1981

Response to plasma perfused over immobilized protein A was investigated in five adenocarcinoma patients for whom conventional therapy had failed. Protein A (0.12 mg, 0.6 mg, 1.25 mg, or 5 mg) was immobilized in 30 g of a collodion-charcoal matrix (PACC). Separated plasma was filtered, perfused through the PACC chamber, and returned to the patient iv. Initially, pain in tumor sites, supraclavicular lymph nodes, or bones was noted in association with hyperemia and edema. Three subjects with five, five, and six perfusions over 42, 10, and 13 days, respectively, showed objective partial remission, improvement of measurable tumors, and tumor cell necrosis. Final tumor reductions of 79.7%, 33.1%, and 66.6%, respectively, were obtained. No objective tumor changes were observed in a patient who received only one perfusion treatment. The fifth patient received plasma from a patient in the initial treatment group and from other adenocarcinoma patients. A final reduction of 57.4% was obtained. Cytarabine, administered to three patients late in the treatment period, had a minimal effect. Toxic effects of treatment included chills, temperature elevation, tachycardia, and pain in tumor sites and chest wall; the effects appeared to be dose-related. Evidence suggests that tumor necrosis may be initiated by cytolytic antibodies found in tumor-bearing plasma after perfusion with PACC. Activation of a natural antitumor defense system appears to be the responsible mechanism. (30 Refs)

26. EFFICACY OF BCG ADJUVANT THERAPY IN BREAST CANCER (MEETING ABSTRACT).

Serrou B, Pujol H, Gary-Bobo J, Cupissol D, Favier F, Favier C
Department of Chemo-Immunotherapy and Laboratoire d' Immunopharmacologie, des Tumeurs INSERM U 236 ERA-CNRS, Montpellier Cedex, France
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Following loco-regional treatment (radiotherapy and surgery), one hundred breast cancer patients (T1-T3: No-N1b) were randomized in two groups: 1) no adjunct treatment or 2) 150 mg Immun BCG-F (Pasteur Institute) po, once a wk for 1 yr. The study has since ended and all patients have been followed for at least 20 mo. No side effects were observed for BCG (vomiting, diarrhea...) necessitating cessation of treatment. After 35 mo, the BCG group shows 20% relapse and no mortality compared to 54% relapse in the control group and 2 deaths. Moreover, the BCG group demonstrated a significant immunorestoration: delayed hypersensitivity skin tests; level of circulating auto-rosette forming cells; natural kilier (NK) activity and anti BCG antibodies. These results confirm that cancer patients in whom immunity was restored to normal levels, have a improved prognosis. (no Refs)

27. SEQUENTIAL VS SIMULTANEOUS TAMOXIFEN (T) AND MEGACE (MEGESTROL ACETATE) (M) IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Forastiere AA, Braum TJ, Wittes RE, Hakes TB, Kaufman RJ
Memorial Sloan-Kettering Cancer Center, New York, NY
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Fifty-six post-menopausal patients (pts) stratified for dominant disease site (soft tissue, osseous, visceral) and estrogen receptor status (positive or unknown) were randomized to sequential T followed on progression by M or simultaneous TM. Dosage was. T 10 mg bid, M 40 mg qid. Forty-six patients are evaluable for response (6 too early). Response is 39% (9/23) T, 17% (4/23) TM. Median time to progression is 9 mo T, 8 mo TM. Analysis of non-stratified variables showed comparable distribution between treatment groups for disease free interval, yr post-menopausal, prior palliative chemotherapy or hormone manipulation, and number of involved organ sites. To date, 17 pts randomized to T (6 responders) have progressed. Nine of these 17 were considered unsuitable for sequential M due to rapidly progressing disease. Results of 8 treated with M are: 1 partial response (T responder), 1 stable, 4 progressions and 2 too early to evaluate. The 1 M responder has been on study for 14+ mo. This includes a response time of 7 mo from start of T to progression, 1 mo off hormone therapy for evaluation of possible rebound response and 6 mo on M. One probable rebound withdrawal response lasting 2.5 mo was observed in a T failure with lung mets. Responses were seen at all dominant disease sites: 6/13 soft tissue, 4/13 visceral (lung), 3/13 osseous. Side-effects were: hypercalcemia-4 pts (2T, 2TM) within 14 days of initiating therapy; vaginal bleeding or discharge-6 pts; host flashes-3 pts; hypertension-4 pts. These preliminary results show that there is no advantage to treatment with TM compared to T alone. A lower response was seen to TM; however, this is not statistically significant. This trial is continuing. (no Refs)

28. CHEMOTHERAPY WITH DIBROMODULCITOL (DBD), ADRIAMYCIN (ADR), CYCLOPHOSPHAMIDE (CYT) FOR METASTATIC BREAST CARCINOMA (MEETING ABSTRACT).

Fraschini G, DiStefano A, Yap HY, Barnes BC, Buzdar AU, Hortobagyi GN, Blumenschein GR
The University of Texas System Cancer Center, M. D. Anderson Hospital, and Tumor Institute Houston, TX
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

DBD was given at 100 mg/m2 po days 1 to 5, ADR at 50 mg/m2 iv day 1, and CYT at 500 mg/m2 day 1 of each 3 wk cycle. ADR was discontinued at a total dose of 450 mg/m2 and substituted by Methotrexate 30 mg/m2 iv day 1 and 8, and 5-fluorouracil 600 mg/m2 iv days 1 and 8. Of 27 evaluable patients (pts), 16 (60%) experienced partial remission (PR), 9 (33%) stabilization of disease (S), and 2 (7%) progression of disease (P). The median duration of PRs and S's was 8 mo. The median survivals were 14.5 mo and 11.5 mo for PRs and S's respectively. Toxicities included myelosuppression, alopecia (100%), nausea and emesis (91%). Three pts (11%) developed congestive heart failure, and one (4%) had an anaphylactic reaction to DBD. The results of this study show that the addition of DBD does not improve the response rate or the duration of response obtained by ADR-CYT alone, or other ADR combinations. (no Refs)

29. DIHYDROXYANTHRACENEDIONE (DHAD), A PROMISING NEW DRUG FOR METASTATIC BREAST CANCER (MEETING ABSTRACT).

Yap HY, Blumenschein GR, Schell F, Valdivieso M, Bodey GP
M. D. Anderson Hospital, Houston, TX
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Based upon the proposal that the amino-sugar group in Adriamycin (Adria) is responsible for its cardiotoxicity, a large number of anthraquinone derivatives was synthesized in an effort to identify a noncardiotoxic compound with a wide spectrum of antitumor activity. In preclinical testing, DHAD possesses antitumor activity equal to or superior to Adria and is less cardiotoxic. We undertook a phase II study to determine the efficacy of DHAD in 33 patients (pts) with refractory metastatic breast cancer who had failed prior treatment with standard drug combinations that included Adria. The median number of prior treatment regimens was 4 (range 2-12) with a median duration of prior therapy of 30 mo (range 4-111). DHAD was given as an iv bolus infusion at a dose of 3-4 mg/m(2)/day x 5, repeated every 28 days. Of the first 26 evaluable pts, there were 1 complete and 5 partial responses (23%); 3 pts had a less than partial response and 5 had stable disease. Responses were seen in soft tissue, lymph node, bone and lung, and appeared to be independent to prior responsiveness to Adria. The median duration of response has not been reached, but is in excess of 4 mo. Congestive cardiac failure was encountered in the single complete responder following 6 mo of therapy with DHAD. Her previous total cumulative Adria dose was 450 mg/m2. Otherwise, nonhematologic toxicity was rare and included mild nausea and vomiting in 6 pts. Granulocytopenia was the most frequently encountered toxic effect and was seen in 50% of the administered courses. (no Refs)

30. DOSE - SCHEDULES OF MEDROXYPROGESTERONE ACETATE FOR BREAST CANCER TREATMENT: A PHARMACOKINETIC APPROACH (MEETING ABSTRACT).

Tamassia V
Farmitalia Carlo Erba, Milan, Italy
Progesterone and Progestins, International Symposium, May 7-9, 1981, Paris, France Centre National de la Recherche Scientifique; 1981

Medroxyprogesterone acetate (MPA) has been shown to be effective in the treatment of several types of cancer, including advanced breast cancer. In this indication, a substantial increase in the response rate was obtained when MPA was given at high doses by im and oral routes. Recent studies revealed the unusual pharmacokinetic profile of MPA which is characterized by a long-lasting depo effect after single im injection and by a fast absorption followed by a rapid elimination after oral administration. As a result of these properties, a different build-up process of blood levels is expected during repeated im or oral administration. The MPA blood level profiles predicted theoretically following treatments at various dosage regimens will be shown. The experimental data obtained in pharmacokinetic studies carried out in breast cancer patients during treatment with MPA by the oral and im routes in good agreement with these theoretically predicted ones. The dosage regimens based on the daily im injection of 500-1000 mg for 4 wk followed by a maintenance therapy with 500 mg/wk are fully rational from a pharmacokinetic point of view as they permit serum MPA levels of 100-200 ng/ml to be attained and maintained during the maintenance period. Equivalent steady-state serum levels can be reached with the oral administration provided that double daily doses are used without reaction during the maintenance period. (no Refs)

31. LOCALIZED HYPERTHERMIA ADJUVANT TO IRRADIATION IN SUPERFICIAL RECURRENT CARCINOMAS: A PRELIMINARY REPORT ON 46 PATIENTS.

Fazekas JT, Nerlinger RE
Dept. Radiation Therapy and Nuclear Medicine, Thomas Jefferson Univ. Hosp., Philadelphia, PA, 19107
Int J Radiat Oncol Biol Phys; 7(10):1457-1463 1981

Combined external microwave (2,450 megaHertz) therapy plus surface heating using a bag with circulating deionized water at 42-44 C has been used in 46 patients (19 males, 27 females) for treatment of superficial recurrent carcinomas. Temperature within a lesion was obtained by insertion of a probe immediately after the microwave generator was turned off. Intralesional temperatures of 41 C have been maintained to depth of 3.0 cm, while most superficial tumor nodules (0 to 2.0 cm) can achieve a temperature of 42.5-43.5 C. Heat is maintained for 30-40 min twice weekly for 6-8 sessions. Adjuvant electron beam radiation of 600-800 rad/wk is used for 3-4 wk. The combined treatment in 36 evaluable patients has resulted in a 50% complete response rate. Highest responses (8/15) were achieved among recurrent superficial tumors masses secondary to chest wall breast adenocarcinoma and within deposits of melanoma. Results of this pilot study are sufficiently encouraging to plan for treatment of advanced, inoperable primary tumor in which less than 50% local control is achievable with all existing modalities (chemotherapy and radiation). (12 Refs)

32. ADJUVANT RADIOTHERAPY IN OPERABLE BREAST CANCER: CORRELATION BETWEEN DOSE IN INTERNAL MAMMARY NODES AND PROGNOSIS.

Strender LE, Wallgren A, Arndt J, Arner O, Bergstrom J, Blomstedt B, Granberg PO, Nilsson B, Raf L, Silfversward C
Radiuhemmet, Karolinska sjukhuset, S-104 01 Stockholm, Sweden
Int J Radiat Oncol Biol Phys; 7(10):1319-1325 1981

In a controlled clinical trial involving 960 patients with operable breast cancer, preoperative radiotherapy (RT) in 316 was compared to modified radical mastectomy followed either by no further treatment (321) or postoperative RT (323). Of the total patients, 654 were followed for greater than 5 yr. Compared to the surgically only treated patients, mortality in those who received preoperative RT was significantly reduced ($p = 0.05$) while mortality in those treated with postoperative RT was only slightly (non-significantly) reduced. In preoperative RT mortality was similar with either the wide field or limited field techniques, while with postoperative RT, only the wide field technique reduced mortality. Preoperative RT significantly improved survival of patients with tumors in the inner half of the breast and with both techniques. The RT dose in the ipsilateral internal mammary nodes was, on the av, lower with the postoperative, than with the preoperative technique. This difference in dose-distribution in the internal mammary nodes is analyzed. (18 Refs)

33. THE OUTCOME OF TREATMENT BY TUMORECTOMY AND RADIOTHERAPY OF PATIENTS WITH OPERABLE BREAST CANCER.

Vilcoq JR, Calle R, Stacey P, Ghossein NA

(c/o Ghossein) Dept. Radiology, Albert Einstein Coll. Medicine of Yeshiva Univ., 1300 Morris Park Ave., Bronx, NY, 10461

Int J Radiat Oncol Biol Phys; 7(10):1327-1332 1981

Survival, local-regional failure and results of salvage surgery were studied retrospectively in 314 patients in two hospitals treated by tumorectomy followed by radiotherapy (RT) for surgically operable breast cancer. Patients were selected who had cancers that could be locally resected without causing significant deformity of the breast. All patients were followed for at least 3 yr. Tumors in 214 patients were 3 cm or less in size and in 74 they were 6 cm or less. The 3-and 5-yr absolute survivals, with no evidence of disease (NED) was 88% (276/314) and 84% (190/225), respectively. About 95% of those who were alive without disease had preserved breasts. Less than 15% were dead or alive with metastatic disease either alone or associated with local recurrences. After 3 and 5 yr, there were 7% (21/314) and 10% (23/225) local-regional failures, respectively. Salvage surgery in 12/14 patients with proven recurrences was either a modified or simple mastectomy; 8/14 were alive with NED after the minimum follow-up period. Local failure was not related to tumor size and was not necessarily associated with disseminated cancer. Tumorectomy followed by RT is an acceptable alternative to mastectomy, particularly since salvage surgery can usually be successfully performed for recurrences. (33 Refs)

34. ANDROGEN-INDUCED REMISSIONS AFTER ANTIESTROGEN AND HYPOPHYSECTOMY IN STAGE IV BREAST CANCER.

Manni A, Arafah BM, Pearson OH

Univ. Hosp. Cleveland, 2074 Abington Rd., Cleveland, OH, 44106

Cancer; 48(11):2507-2509 1981

Fluoxymesterone (Halotestin), 10 mg po BID, was given to 33 women with Stage IV breast cancer who had previously been treated with the antiestrogen tamoxifen (Nolvadex) and of whom 17 had also undergone hypophysectomy. Objective remissions were obtained in 13 patients (39%) with an av duration of 11+ mo. Response rate to fluoxymesterone was similar in patients who had previously responsed to tamoxifen and in those who had failed. Duration of response was longer in the former group (12+ vs 8 mo), but this difference was not statistically significant. Of 17 patients who had been previously treated with tamoxifen and hypophysectomy, 7 obtained further remission from fluoxymesterone for an av duration of 10 mo. Two patients with remissions from fluoxymesterone had previously failed to respond both to antiestrogen therapy and to the removal of the pituitary gland. Androgens appear to be an effective sequential endocrine treatment of Stage IV breast cancer after tamoxifen and hypophysectomy. The mechanism by which androgens induce tumor regression in some patients is probably not an antiestrogenic effect or an indirect effect mediated through the pituitary gland, but perhaps a direct action at the tumor level. (Author abstract) (11 Refs)

35. ELASTOSIS IN HUMAN BREAST CANCER AND RESPONSE TO ENDOCRINE THERAPY (MEETING ABSTRACT).

Masters JR, Millis RR, King RJ, Minton M, Rubens RD
Institute of Urology, St. Pauls Hospital, London WC2, England
Br J Cancer; 43(5):718 1981

The amount of elastosis in primary breast tumors was found to be associated with response to endocrine therapy in a preliminary study of a small series of cases. In order to confirm this finding in histological sections from the primary tumors of 245 patients with advanced breast cancer, elastosis was subjectively assessed as absent, present in small or moderate amounts, or present in gross amounts. The patients received a total of 289 endocrine treatments assessable using UICC criteria (oophorectomy, 38; ovarian irradiation, 22; androgens, 45; estrogens, 37; hypophysectomy, 32; tamoxifen, 115). In the women whose tumors did not contain elastosis there were 8/56 (14%) responses, in contrast to 13/31 (42%) in those with gross elastosis. The assessment of elastosis is a simple exercise which requires no additional material, and these data confirm that there is an association between elastosis in primary breast tumors and the response to endocrine therapy for advanced disease. (1 Ref)

36. BODY WEIGHT AND PROGNOSIS IN BREAST CANCER.

Boyd NF, Campbell JE, Germanson T, Thomson DB, Sutherland DJ, Meakin JW
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, M4X 1K9, Canada
JNCI; 67(4):785-789 1981

We have examined the relationship between risk factors for breast cancer incidence and the subsequent prognosis of breast cancer among patients in a randomized controlled trial of adjuvant ovarian ablation. Body wt was the only risk factor found to be associated with statistically significant differences in survival. This finding could not be explained by a disproportionate number of anatomically more advanced tumors in the heavier women. In premenopausal women aged 45 yr or more, the only group to benefit from adjuvant ovarian ablation, there was an interaction of treatment and wt, suggesting that wt exerts its influence on prognosis by a hormonal mechanism. The prognostic effect of wt was generally most marked in patients with tumors whose prognostic characteristics were favorable, and in these patients wt loss as an adjuvant treatment may reduce the frequency of disease recurrence. (Author abstract) (22 Refs)

SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)

37. LUMPECTOMY AND CHEMOTHERAPY: UNPROVED METHOD OF TREATING BREAST CANCER.

Pressman PI
Dept. Surgery, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY, 10003
NY State J Med; 81(12):1765-1767 1981

Some confusion exists today among patients and their physicians as to how to treat a breast cancer when the patient refuses a mastectomy or the operation seems inadvisable for medical reasons. Lumpectomy, followed by chemotherapy, is occasionally performed as the only other treatment modality. This is a misinterpretation of the role of adjunctive chemotherapy, which is properly administered, in addition to adequate local therapy (mastectomy or radiation therapy) to treat micrometastases in patients whose axillary lymph nodes are positive for cancer. Two cases are presented which demonstrate persistent growth of carcinoma in the breast where the only treatment was lumpectomy and chemotherapy. It is not yet possible to select chemotherapeutic agents that can substitute for adequate local treatment. (Author abstract) (6 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

38. CANCER RISK AND OESTROGEN METABOLISM IN MENOPAUSAL WOMEN (MEETING ABSTRACT).

James VH, Reed MJ
Department of Chemical Pathology, St. Mary's Hospital Medical School, London W2 1PG, England
Fifth International Symposium of the Journal of Steroid Biochemistry, July 13-15, 1981, Puerta Vallarta, Jalisco, Mexico. Journal of Steroid Biochemistry 80 pp., 1981.

Many studies have been carried out to compare plasma and urinary estrogen levels in women with endocrine associated cancers and healthy controls, but no consistent abnormality has been found. As it is possible that there may be differences which are not revealed by measurement of urinary or plasma concentrations, a study is being carried out, using a double isotope technique, to measure the production rates of estrogens in menopausal women with endometrial cancer (EC) or endometrial hyperplasia - (EH). In addition the percent unbound estradiol is being measured in women with benign or malignant breast disease. The metabolic clearance rate (MCR) for estradiol in women with EC was significantly higher than in women with EH. No significant difference has so far been found for the MCR estrone. Production of estrone was elevated in obese women with EC or EH, but an elevated production of estradiol was only seen in one subject studied close to the menopause. The percent unbound estradiol in menopausal women with malignant breast disease was significantly higher than in normal women or those with benign breast disease. A significant difference was still found when subjects were matched for wt. It is concluded that although measurements of urinary or plasma levels of estrogens have failed to reveal any abnormality, the increased clearance and percent unbound - estradiol found for cancer subjects in the present study suggest that tissues of subjects with cancer may be exposed to greater estrogenic stimulation than normal subjects. (no Refs)

39. THE RELATIONSHIP BETWEEN DIETARY FAT AND HORMONES IN MAMMARY CARCINOGENESIS (MEETING ABSTRACT).

Dao TL
Roswell Park Memorial Institute, Buffalo, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both epidemiologic findings and experimental data provide convincing evidence to support the concept that the etiology of cancer is multifactorial. In experimental mammary carcinogenesis, polypeptide and steroid hormones have been shown to be involved in the initiation and promotion phases of mammary tumor induction. Among the environmental factors suspected to play a role in mammary carcinogenesis, dietary fat correlates well with breast cancer incidence. This paper will present experimental data to demonstrate the co-carcinogenic effect of hormones in the induction of mammary cancer in the rat by polycyclic aromatic hydrocarbons. The experimental data will be compared with human epidemiologic findings. The relationship between dietary fat and mammary carcinogenesis in experimental models will be presented and, finally, the possible relationship between dietary fat and hormones will be discussed. (no Refs)

40. INDEPENDENT RISK FACTORS OF BENIGN AND MALIGNANT BREAST LESIONS.

Soini I, Aine R, Lauslahti K, Hakama M

Dept. Public Health, Univ. Tampere, Box 607, 33101 Tampere 10, Finland

Am J Epidemiol; 114(4):507-514 1981

The purpose of this study is to evaluate the risk factors of benign breast disease and to compare them with the known risk factors of breast cancer in order to make inferences on the relationship between benign breast disease and breast cancer. All benign breast lesions diagnosed from the population of the city of Tampere, Finland in 1974-1977 were reclassified by two pathologists into two groups of dysplasia and two groups of tumors. In the risk analysis of 422 age-matched pairs no group of benign lesions had risk factors consistently similar to those of breast cancer. it is therefore likely that either benign breast disease is not associated with breast cancer or it is an independent risk factor, not associated with the other high risk indicators of breast cancer. (Author abstract) (34 Refs)

41. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

Epidemiology of benign breast disease (BBD) is reviewed. Topics include BBD (the problem of case definition), estimates of the occurrence of BBD, evidence for an association of BBD and breast cancer, interaction of BBD and other risk factors for breast cancer, and factors associated with BBD (age, race, socioeconomic status, menstrual and reproductive characteristics, family history of breast cancer, obesity, endogenous hormone levels, and exogenous hormone use). Published data for the occurrence of BBD, risk of breast cancer associated with BBD, relative risk of breast cancer associated with various factors among women with and without BBD, menstrual and reproductive factors in relation to BBD, and biopsy-defined BBD and oral contraceptive use are summarized. Evidence suggests that risk of breast cancer associated with various factors may be greater in women with BBD than in those with no such history; inconsistencies across epidemiologic studies may result from a lack of analyses specific to histopathologic type of benign disease. (79 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

42. STUDIES OF THE ENDOCRINE, PARACRINE AND AUTOCRINE CONTROL OF MAMMARY TUMOR CELL GROWTH (MEETING ABSTRACT).

Leland FE, Danielpour D, Sirbasku DA

Department of Biochemistry and Molecular Biology, The University of Texas Medical School, Houston, TX

Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Classical endocrine studies have shown that both estrogens and prolactin are required for growth of several types of carcinogen induced mammary tumors of experimental animals. However, despite the best efforts by many laboratories, the dramatic trophic effects of these hormones seen in vivo have been elusive in vitro. Our data, obtained with the MTW9/PL rat mammary tumor cell line, as well as data obtained by others with the MCF-7 and T47-D human mammary tumor lines, have shown that estrogens are required for optimum tumor formation by these cells in vivo, but either no or minimal mitogenic effects of estrogens are demonstrable in culture. To reconcile this observation, we have asked whether estrogen-regulated growth factors may be involved in mammary tumor growth in vivo. We have considered three possible mechanisms by which this process may occur: endocrine control; paracrine control; and autocrine control. We conclude from our studies that all three mechanisms may function in vivo, and that in addition, the differences between estrogen-responsive mammary tumor growth in vivo and autonomous growth in vivo may be related to the ability of the autonomous cells to produce paracrine/autocrine type growth factor constitutively. (no Refs)

43. IN VITRO INHIBITORY EFFECT OF INTERFERON ON DNA SYNTHESIS OF BREAST CANCER CELLS AND RELATIONSHIP TO STEROID RECEPTORS (MEETING ABSTRACT).

Jakesz R, Kerjaschki D, Kolb R, Reiner G, Spona J, Swetly P
University of Vienna, A-1090 Vienna 9, Austria
Eur Surg Res; 13(1):31 1981

For selecting patients for postoperative interferon treatment we carried out the following in vitro study. From 22 patients with primary or recurrent breast cancer, fresh tumor tissue was obtained. Tissue cultures were prepared from mouse bone marrow cells according to the method of Dexter et al, and used as a feeder layer for cultivation of breast cancer cells in a humified atmosphere. At least 48 hr after incubation, confluent tumor cell colonies could be determined and the cells could be differentiated as epithelial using electron microscopy. For determining the influence of interferon DNA synthesis 3H-thymidine uptake was measured after incubation of breast cancer cells with interferon or without for control. Human lymphoblast interferon (HLI) was obtained from Namalwa cells after induction by Sendai virus. Human fibroblast interferon (HFI) was induced in human fibroblasts by Poly I:C and purified by controlled pore glass chromatography. Ten and 100 U/ml interferon were used. Forty-eight hr after incubation with interferon 3H-thymidine was measured. (1) An optimal reduction of DNA synthesis could be achieved in 32% with 100 U/HFI and in 62% with the same dose of HLI. (2) Using only 10 U interferon, only suboptimal reductions were seen. (3) 22% of ER+ culture cells show a marked reduction of DNA synthesis compared with 50% ER- cells. These results indicate that 100 U HLI is more effective than the same dose of HFI. The higher response rate of cells or ER tumors could be an argument for selecting ER- patients for interferon therapy. (3 Refs)

44. MONOCLONAL ANTIBODIES TO DIFFERENTIATION ANTIGENS OF NORMAL HUMAN MAMMARY EPITHELIAL CELLS (MEETING ABSTRACT).

Peterson JA, Moncada FR, Ceriansi RL
Bruce Lyon Memorial Research Laboratory, Children's Hospital Medical, Center 51st and Grove Streets, Oakland, CA, 94609
In Vitro; 17(3):225 1981

Hybridomas were prepared that secrete monoclonal antibodies to surface antigens of normal human mammary epithelial (HME) cells by fusion of mouse myeloma cells with spleen cells from BALB/c mice immunized with human milk fat globule (HMFG) membranes. Preliminary selection for presumptive breast specificity was based on specific binding to HMFG membranes and not to membranes from human mammary fibroblasts, or HeLa, HT-29, or lymphoblastic cell lines. Specificity of binding to HME cells was shown by competion with solubilized HMFG and with rabbit anti-HME antisera. Five different hybridomas have been prepared, all of which bind to surface antigens of normal HME cells while each binds differently to several human breast carcinoma cell lines, thus indicating a heterogeneity in surface antigens of breast tumors. We have previously shown that the HMFG membrane is made up of four major components, three of which contain antigens specific for HME cells. The monoclonal antibodies bind to at least two different mol wt components. These hybridomas will be useful in characterizing surface antigens of normal HME cells and in classifying breast tumors. (1 Ref)

45. HUMAN MAMMARY EPITHELIUM IN CULTURE (MEETING ABSTRACT).

Smith HS, Hackett AJ, Ceriani R, Stampfer MR
Peralta Cancer Research Institute, Berkeley, CA, 94720
In Vitro; 17(3):203 1981

Our laboratory has developed a culture system for studying carcinogenesis of human mammary epithelium. We can now readily culture over 90% of specimens representing various stages of malignant progression including reduction mammoplasties, peripheral mastectomy tissue, primary carcinomas, and hypodermal metastases. Briefly, mammary tissue is enzymatically dissociated from stromal elements, separated by filtration and cryopreserved. Utilizing an enriched media plus cholera toxin, the epithelial cells can be grown in mass culture with doubling x of 24-48 hr and can be subcultured approx 1-4 x at a 10 fold dilution. By plating on irradiated fibroblasts in enriched media, single epithelial cells develop into colonies with plating efficiencies ranging from 6-40%. The cells are identified as epithelial by electron microscopy, by the presence of domes and ridges, by a distinctive abbreviated fibronectin pattern and by the presence of mammary epithelial antigen. To elucidate the nature of malignant transformation, we have begun to compare the properties in culture of the normal and malignant cells. There are subtle differences in morphology with the most notable being an increased nuclear:cytoplasmic ratio in the tumor cells. The tumor and normal cells also differ in colony morphology. The normal cells form an organized noninvasive colony while the malignant specimens contain a population of colony forming cells that invade the stromal feeder layer. (1 Ref)

46. INHIBITORY ACTION OF ASPARAGUS RACEMOSUS ON DMBA-INDUCED MAMMARY CARCINOGENESIS IN RATS.

Rao AR
Cancer Biology Lab., Sch. Life Sci., Jawaharlal Nehru Univ., New Delhi-110 067, India
Int J Cancer; 28(5):607-610 1981

The present paper reports the inhibitory effect of Asparagus racemosus on DMBA-induced mammary tumorigenesis in rats of Holtzman strain. When virgin female rats, normal or primed with 17-beta-estradiol treatment, are put on diets containing 0.25%, 0.5%, 1% or 2% Asparagus root extract powder prior to their exposure to DMBA, mammary tumor incidence shows a sharp decline. (Author abstract) (39 Refs)

47. THE USEFULNESS OF HYPERTHERMIA AS ADJUVANT TO RADIOTHERAPY STUDIES ON A TRANSPLANTABLE MAMMARY CARCINOMA (MEETING ABSTRACT).

Wondergem J, Haveman J
Department of Radiotherapy, Wilhelmina Gasthuis, le Helmersstraat 104, 1054 EG Amsterdam, The Netherlands
Strahlentherapie; 157(9):624 1981

The sensitivity of tumors of a tranplantable murine mammary adenocarcinoma for heat combined with X-irradiation was studied in function of the tumor-vol by evaluating growth delay and cure. In the range of tumor-vol studies, 0.1-0.4 cm3, there is a progressive decrease of the radiosensitivity at increasing tumor-vol. In unanesthetized mice this phenomenon can largely be explained by the appearance of hypoxic cells in the tumor during growth. The appearance of hypoxic cells was evaluated by studying the effects of the hypoxic cell sensitizer misonidazole. Chronically hypoxic cells in these tumros appeared to be selectively sensitive to hyperthermia (60 min at 43 C) compared to well-oxygenated cells, whereas acutely hypoxic cells did not show an enhanced sensitivity to heat. Pentobarbital sodium anesthesia (50 mg/kg ip) of the animals caused acute hypoxia in those tumors where already a hypoxic cell fraction could be found. The anesthesia thus led to a negative influence on the thermal enhancement of radiation effects observed at the investigated tumor-vol. Potentiation of radiation effects independent of the selective action of heat on chronically hypoxic cells was not found in our experiments. This in spite of the fact that hyperthermia was applied immediately after irradiation. Misonidazole (0.5 g/kg ip), when administered prior to the heat-treatment did not affect the thermosensitivity of the tumor-cells. In the combined irradiation-heat treatment and enhanced cytotoxicity of chronically hypoxic cells to misonidazole emerges. Misonidazole does not show an enhanced cytotoxicity to acutely hypoxic cells. (no Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Aine R.	40
Albrechtsen R.	8
Anderson B.	22
Arafah BM.	34
Arndt J.	32
Arner O.	32
Autuoro LM.	14
Ayus C.	25
Azevedo D.	15
Baker RR.	18
Barnes BC.	20
Barnes BC.	28
Barnes DM.	10
Barrett DL.	4
Baulieu EE.	9
Bergstrom J.	32
Betsill WL.	5
Blamey RW.	11
Blamey RW.	12
Blomstedt B.	32
Blumenschein GR.	20
Blumenschein GR.	28
Blumenschein GR.	29
Bodey GP.	29
Boller B.	24
Boyd NF.	36
Braum TJ.	27
Braun DW.	6
Braun DW.	7
Brockmeyer D.	14
Buchholz R.	2
Burgess MA.	20
Buzdar AU.	20
Buzdar AU.	28
Calle R.	33
Campbell FC.	12
Campbell JE.	36
Carson EJ.	14
Cerianai RL.	44
Ceriani R.	45
Chawla RK.	23
Chew K.	4
Chou TH.	17
Cook G.	25
Cooke T.	13
Coombes RC.	17
Critselis AN.	14
Croton R.	13
Cupissol D.	26
Danielpour D.	42
Dao TL.	39
Daskal Y.	25
Degenshein GA.	14
DiStefano A.	28
Doepp M.	21
Dube VE.	22
Duda V.	2
Elston CW.	12
Engvall E.	8
Ernster V.	4
Ernster VL.	41
Espada R.	25
Eulenburg R.	2
Favier C.	26
Favier F.	26
Fazekas JT.	31
Feldman L.	25
Finkle WD.	15
Forastiere AA.	27
Forrest AP.	16
Fracchia AA.	7
Fraschini G.	28
Frederiksen P.	19
Frommer P.	25
Gary-Bobo J.	26
George D.	11
George WD.	13
Germanson T.	36
Ghossein NA.	33
Glass A.	15
Granberg PO.	32
Griffiths K.	11
Griffiths K.	12
Griffiths K.	13
Hackeloer BJ.	2
Hackett AJ.	45
Hakama M.	40
Hakes TB.	27
Harris M.	10
Haveman J.	47
Hawkins RA.	16
Haybittle JL.	12
Henry JF.	25
Hisada Y.	1
Holt S.	13
Hoover R.	15
Hortobagyi GN.	20
Hortobagyi GN.	28
Howat JM.	10
Howell JF.	25
Huneke B.	2
Iinuma K.	1
Iwaki Y.	22
Jakesz R.	43
James VH.	38
Karcher KH.	24
Kashida R.	1
Kaufman RJ.	27
Kerjaschki D.	43
Kessel DH.	17
King EB.	4
King RJ.	35
Kinne DW.	6
Kinne DW.	7
Kolb R.	43
Lagergren C.	3
Laubenberger Th.	21
Lauslahti K.	40
Lauth G.	2
Lawson DH.	23
Lehane C.	25
Leland FE.	42
Levy C.	9
Liljevall S.	3
Manni A.	34
Masters JR.	35
Matsukawa M.	1
Mattioli C.	25
McDowell K.	14
Meakin JW.	36
Miller FW.	23
Miller L.	25
Miller WR.	16
Millis RR.	35
Milne K.	15
Minton M.	35
Moncada FR.	44
Mortel R.	9
Namer M.	9
Nerlinger RE.	31
Nicholson RI.	11
Nicholson RI.	12
Nicolson R.	13
Nielsen M.	8
Nilsson B.	32
Paone JF.	18
Pearson OH.	34
Peterson JA.	44
Petrakis NL.	4
Poulsen HS.	19
Pressman PI.	37
Pujol H.	26
Raf L.	32
Rao AR.	46
Reed MJ.	38
Reiner G.	43
Richmond A.	23
Robel P.	9
Rosen PP.	6
Rosen PP.	7
Rubens RD.	35
Rudman D.	23
Ruoslahti E.	8
Saigo PE.	6
Saigo PE.	7
Schell F.	29
Schell FC.	20
Serrou B.	26
Shaper JH.	18
Shearer WT.	25
Silfversward C.	32
Sirbasku DA.	42
Smith HS.	45
Soini I.	40
Spona J.	43
Stacey P.	33
Stampfer MR.	45
Strender LE.	3
Strender LE.	32
Sutherland DJ.	36
Swetly P.	43
Swindell R.	10
Takamizawa K.	1
Takehara Y.	1
Tamassia V.	30
Terasaki P.	22
Terman DS.	25
Thomson DB.	36

Tillquist R. 25
Valdivieso M. 29
Vilcoq JR. 33
Waalkes TP. 18
Walker AN. 5
Wallgren A. 3
Wallgren A. 32
Weathers E. 6
Weathers E. 7
Wewer U. 8
Wittes RE. 27
Wondergem J. 47
Yamamoto T. 25
Yap HY. 20
Yap HY. 28
Yap HY. 29
Young JB. 25
Zaleski HI. 25

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS) 1
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS 2-9
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS 10-15
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS 16
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY) 17-25
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY 26-28
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY) 29-34

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HE 20. 3173/2:

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. DETECTING BREAST CANCER AT HOME.

Karpman HL, Hamilton B
Dept. Medicine, Univ. California Sch. Medicine, Los Angeles, CA
Diagn Med; 4(8):9-11 1981

A thermographic device called a Breast Cancer Screening Indicator (BCSI) is described which is simple enough for the patient to wear at home for 15 min each mo. The BCSI appears capable of detecting lesions earlier than palpation. Thermosensitive units on the device change color in reaction to abnormal warmth and alert the patient and her physician to possible tumors. In clinical trials of the device, false negatives have occurred at approx 10% and false positives at 15%. (12 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. MAMMARY LYMPHATIC SCINTISCANS BY INTRATUMORAL INJECTION IN THE ASSESSMENT OF BREAST CANCER: 105 EXAMINATIONS IN 100 PATIENTS.

Gabelle P, Comet M, Bodin JP, Dupre A, Carpentier E, Bolla M, Swiercz P
Service de Chirurgie Generale et Digestive, C.H.U., Hopital des Sablons, F 38043 Grenoble Cedex, France
Nouv Presse Med; 10(37):3067-3070 1981

One hundred and five scintiscans of the mammary lymphatic system were performed in 100 patients with breast cancer by intratumoral injection of 99 m Tc-labeled colloidal rhenium. The progression of the radioactive colloidal agent was followed on a series of films taken 1, 2, and 4 hr after the injection, and the images obtained were compared with postoperative findings of lymph node involvement. Patients with more than three carcinomatous lymph nodes had less than two foci of activity, while those with less than three carcinomatous lymph nodes had more than two foci of activity, owing to more rapid progression of the compound. The difference was highly significant (p less than 0.001). (Author abstract) (12 Refs) (In FRE)

3. RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA. II. PROGNOSTIC CONSIDERATIONS ON THE BASIS OF A SHORT-TERM FOLLOW-UP.

Andersson I
Dept. Diagnostic Radiology, Univ. Lund, Malmo Allmanna Sjukhus, S-21401 Malmo, Sweden
Acta Radiol [Diagn] (Stockh); 22(3A):227-233 1981

Prognostic markers were analyzed in a randomized screening project for breast carcinoma using mammary radiography as the only screening method. The proportion of small carcinomas (non-invasive carcinoma and invasive at most 10 mm across) was significantly larger among carcinomas detected at screening than that of carcinomas appearing in the control group. Furthermore, the rate of axillary metastasis was lower and the proportion of stage I disease significantly larger. The proportion of highly differentiated tubular carcinoma and intraductal carcinoma in situ was significantly larger in the screened group, while the proportion of less differentiated tubuloductal carcinoma, invasive comedocarcinoma and medullary carcinoma with lymphoid infiltration was larger in the comparison group. The findings strongly indicate that carcinomas found at radiographic screening represent, on the av, an earlier stage compared with carcinomas detected in clinical practice. (Author abstract) (12 Refs)

4. DIAGNOSTIC ACCURACY OF XEROMAMMOGRAPHY.

Castiglione V, D'Antona A, Dellafiore L, Ferrario L, Luzzatti G, Mortara G, Pizzinelli P, Vitali T
(c/o Luzzatti) Servizio di Radiologia, Ospedale San Carlo Borromeo, Via Pio II 3 , 20153 Milano, Italia
Tumori; 67(5):447-453 1981

The analytical study of the case material has allowed a precise evaluation of the distribution by age groups of the different pathologic processes of the breast, of the localizaton and dimensions of malignant tumors, as well as the diagnostic accuracy for those cases histologically ascertained and those with a follow-up. The diagnostic accuracy and the consequent reliability of the xeroradiographic method for the diagnosis of breast cancer is distinctly superior to that reported in the literature for traditional mammography, whereas for the differential diagnosis between circumscribed dysplastic manifestations and benign tumors xeromammography is not sufficiently reliable. The authors critically discuss the results and in particular the problem of false positives, which also include diagnostic errors that cannot be avoided in that they directly derive from the pathologic morphology of the disease process (plasma cell mastitis and sclerosing adenosis). As regards the problem of false negatives, they can be reduced within certain limits by resorting to other instrumental investigations. However, there are cases (1% of the malignant neoplasias histologically ascertained) that present a completely negative xeroradiographic finding. These are the limits of the radiologic investigation which cannot in any way be surmounted. (Author abstract) (15 Refs)

5. PALPABLE BREAST MASSES. THE IMPORTANCE OF PREOPERATIVE MAMMOGRAPHY.

Kopans DB, Meyer JE, Cohen AM, Wood WC
Dept. Radiology, Massachusetts General Hosp., Boston, MA, 02114
JAMA; 246(24):2819-2822 1981

Mammography has a significant role to play before any breast surgery is performed. Ten cases are described to illustrate five benefits: (1) confirm the presence of an evident neoplasm, (2) define the three breast masses that do not require biopsy, (3) demonstrate ipsilateral multicentricity of breast cancer, (4) discover occult contralateral cancer, and (5) detect occult malignant neoplasia elsewhere in a breast having a mass excised or reconstruction performed. (Author abstract) (7 Refs)

6. FIBROADENOMA OF THE BREAST: 123 CASES.

Cunsolo A, Scandellari S, Zanni E, Maldarizzi F, Vecchi R, Vitolo A
Istituto di Clinica Chirurgica I, Universita di Bologna, Bologna, Italy
Minerva Chir; 36(18):1195-1198 1981

Between 1956-1976, of 284 benign mammary pathology cases, 123 fibroadenomas were observed. Histological preparations were reexamined and all patients came for control visits. Eighteen patients had to be eliminated due to incomplete records, 7 patients died: 3 due to unknown causes, 3 due to unrelated causes, and 1 due to multiple metastases of lobular infiltrating carcinoma, which started from mammary fibroadenoma.

A woman (37 yr old), had since puberty a nodule on the left breast that was not painful and was never resected. At surgery the nodule had a diameter of 5 cm. Left mastectomy with axillary nodules removal was performed, but the patient died 9 mo later. Fibroadenomas started between 14-66 yr, av age was 28 yr. Forty five percent of the patients had one or more pregnancies before fibroadenomas developed. Familiar mammary pathology was present in 27.5%. A second fibroadenoma appeared and was surgically removed in 23.5% of cases. At control visit 31.3% of patients had mastopathies. (7 Refs) (In ITA)

7. MILK OF CALCIUM WITHIN TINY BENIGN BREAST CYSTS.

Sickles EA, Abele JS
Dept. Radiology, M-396, Univ. California Sch. Medicine, San Francisco, CA, 94143
Radiology; 141(3,part1):655-658 1981

Small amounts of milk of calcium settling to the bottom of multiple tiny benign breast cysts produce the mammographic picture of clustered linear and curvilinear calcifications when imaged in lateral projection with a horizontal x-ray beam. These calcifications, although benign, may be confused with the microcalcifications of carcinoma. Milk of calcium is found much more frequently in small breast cysts than anywhere else in the body. It is not at all uncommon, occurring in more than 4% of women undergoing diagnostic mammography. Fortunately, the overall mammographic appearance of milk of calcium cysts is quite characteristic, permitting them to be a differentiated from malignant breast microcalcifications with a high level of confidence. (Author abstract) (13 Refs)

8. THE DIAGNOSTIC AND THERAPEUTIC VALUE OF BREAST CYST PUNCTURE AND PNEUMOCYSTOGRAPHY.

Tabar L, Pentek Z, Dean PB
Radiologic Clinic, Medical Univ., Pecs, Hungary
Radiology; 141(3,part1):659-663 1981

Out of 53,459 women undergoing mammography, 434 pneumocystographic examinations were performed in 338 patients. Thirteen benign and 13 malignant intracystic tumors were detected, for a frequency of 6.0%. Intracystic cancers comprised 1.3% of all malignant tumors. Neither visual nor cytological examination of cyst fluid was sufficient to detect or rule out cancer, and the authors feel that pneumocystography is the only reliable method. Excision is the preferred therapy, and histological examination is the definitive method of differentiating benign from malignant tumors. In more than 97% of cases, pneumocystography of simple cysts is therapeutic. Without evidence of intracystic tumor on pneumocystography, cyst removal is unnecessary. The patient can be followed up with mammography, and any recurrent or new cysts can be diagnosed and treated by pneumocystography alone. (Author abstract) (17 Refs)

9. SHORT TERM ORGAN CULTURE OF HUMAN BREAST TUMOUR TISSUE AND ITS APPLICATION IN STUDIES OF STEROID METABOLISM.

Duncan JN, Davis JC, Wade AP, Walker S
Sub-Dept. Endocrine Pathology, Univ. Liverpool, Alder Hey Hosp., Liverpool L12 2 AP, England
Eur J Cancer Clin Oncol; 17(10):1133-1142 1981

A method of organ culture capable of maintaining explants of human breast tumors for 3 days, as evidenced by comparison of the tumor histology before and after culture, is described. In general, survival was good, although cultures of scirrhous tumors were less successful. A commercial culture medium, Ham's F10, was used without serum addition but with the addition of insulin. Tumor tissue was cultured with 4-[14C]-cholesterol (11 cases), 4-[14C]-pregnenolone (3 cases) and 1beta,2beta-[3H]testosterone (3 cases). The existence of desmolase and aromatase enzyme systems in breast tumor tissue is suggested by the separation of neutral, acidic and phenolic fractions from cholesterol and pregnenolone cultures. Metabolites have not yet been identified. Further evidence of aromatase activity is given by the formation of [3H]-water from 1beta,2beta-[3H]-testosterone. (Author abstract) (31 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

10. ESTROGEN RECEPTOR QUANTITATION AND STAGING AS COMPLEMENTARY PROGNOSTIC INDICATORS IN BREAST CANCER: A STUDY OF 583 PATIENTS.

Godolphin W, Elwood JM, Spinelli JJ
Div. Clinical Chemistry, Vancouver General Hosp., Vancouver, B.C., Canada
Int J Cancer; 28(6):677-683 1981

Estrogen receptor (ER) quantity was measured at the time of primary diagnosis on 583 patients with breast cancer seen at the major treatment center in British Columbia between 1975 and 1979. Survival rates (overall, recurrence-free and post-recurrence) were assessed relative to ER concentration, staging, menopausal status, age, differentiation, and therapy. A linear trend in increased survival was demonstrable through variations in ER concentration from less than or equal to to greater than or equal to 260 fmoles/mg cytosol protein. This trend was highly significant and remained after adjustment for stage, menopausal status, and age, and was seen for all groups of patients except those with metastatic disease. The association of high ER concentration with increased recurrence-free survival was not due to differing response to adjuvant therapy, but the trend in post-recurrence survival was only significant in patients who had received hormonal therapy. Survival was as strongly associated with receptor concentration as with staging, and these two factors were almost completely independent. A proportional hazards model was fitted to produce predictions of survival, and showed that TNM Stage III patients with high ER concentrations have a better survival than Stage I or II patients with lower ER concentrations. This suggests that quantitative assessment of ER status is essential to definition of risk in breast cancer patients and that stratification in clinical trials and consideration for adjuvant therapy ought to be guided, in part, by a standardized ER-quantitative determination performed on the primary tumor. (Author abstract) (34 Refs)

11. DETERMINATION OF TAMOXIFEN AND BIOLOGICALLY ACTIVE METABOLITES IN HUMAN BREAST TUMOURS AND PLASMA.

Daniel P, Gaskell SJ, Bishop H, Campbell C, Nicholson RI
Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Heath Park, Cardiff, CF4 4XX, Wales
Eur J Cancer Clin Oncol; 17(11):1183-1189 1981

This work describes the measurement of the antiestrogenic drug, tamoxifen, and two of its biologically active metabolites in the plasma and tumor tissue of patients with primary breast cancer. All three compounds were detected at high concentrations relative to those of estradiol, with which tamoxifen competes for binding to specific receptors in tumor cells. N-desmethyltamoxifen was the more abundant metabolite in both plasma and tissue, where its concentration exceeded that of the parent drug. An hydroxylated metabolite, metabolite B, was present at about 2% the concentration of tamoxifen in both plasma and tumors. The high concentrations of these compounds measured in human tissue were therefore similar to those previously found to be capable of preventing the specific binding of estradiol to its receptors in vitro. (Author abstract) (23 Refs)

12. PLASMINOGEN ACTIVATOR ACTIVITY AND COMPOSITION IN HUMAN BREAST CANCER.

Evers JL, Patel J, Madeja JM, Schneider SL, Hobika GH, Camiolo SM, Markus G
(c/o Markus) Dept. Experimental Biology, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263
Cancer Res; 42(1):219-226 1982

The plasminogen activator activity of human breast tumors was determined quantitatively in extracts of 33 primary tumors, 11 lymph node metastases, and 11 normal tissues. Activities varied more widely in the neoplastic tissues than in the normal ones. The mean activator content of the tumors (primary and metastasis) was significantly higher (p greater than 0.01) than that of normal tissues: 4.4-fold on a g wet tissue basis and 2.1-fold when the activities were referred to the protein content of the extracts. Primary and metastatic tumors were not significantly different from one another in their plasminogen activator content. In the six cases where tumors and normal tissue pairs from the same patients could be compared, the mean of the individual tumor:normal ratios was 10.0 (wet wt) or 3.6 (extract protein). In addition to the activator content, the molecular type of the enzymes was also determined, using goat antibody formed against human urinary urokinase as an inhibitor of activator activity. On the av, 80% of the activity of the tumor extracts could be inhibited by the antibody; extracts of normal breast tissue contained only 62% urokinase-like activator. The activators were also characterized by sodium dodecyl sulfate gel electrophoresis using two different methods for the zymographic visualization of activator bands. The fraction of urokinase-like enzyme determined by the fibrinogen copolymerization method agreed well with the results obtained by immunoinhibition. No correlation was found between activator activity or activator composition, on the one hand, and the degree of differentiation of the tumors, the fraction of positive lymph nodes found, or the amount of estrogen-binding protein (or their molecular size) in the cytosol of the tumors, on the other. This apparent lack of correlation may reflect variations in local physiological conditions which necessitate the presence of widely differing amounts of activator in order to ensure a critical amount of the product of the reaction catalyzed by this enzyme, ie, plasmin. (Author abstract) (37 Refs)

13. LEVELS OF POLYAMINES AND NUCLEIC ACIDS IN HUMAN BREAST CARCINOMA.

Romano M, Cecco L, Cerra M
Istituto Tumori, Via Mariano Semmola, 80131 Napoli, Italia
Tumori; 67(5):431-435 1981

Polyamine and nucleic acid levels were determined in normal human breasts, in primary infiltrating ductal carcinoma breasts, in the uninvolved tissues of the same carcinoma-bearing breasts and in the urine of the same patients. The results showed that the production of polyamines in the carcinoma tissue is significantly higher than in normal tissue; the presence of a carcinoma in the breast does not modify the levels of polyamines and nucleic acids in the surrounding uninvolved tissue; spermidine and spermine are correlated both with DNA and RNA in the carcinoma; the urinary polyamine levels in the carcinoma-bearing patients were not significantly different from that of controls. There appeared to be a close relationship between polyamine biosynthesis and tumoral mammary cell development and a very fine control between the biosynthesis of both spermidine and spermine and nucleic acids. In addition, the localized solid breast carcinoma, with non-proven metastases, did not provoke an increase in polyamine excretion. (Author abstract) (25 Refs)

14. THE CYTOCHEMICAL DEMONSTRATION OF OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

Walker RA
Dept. Pathology, Univ. Leicester, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, England
J Pathol; 135(3):237-247 1981

Presence of estrogen receptors (ER) in human breast carcinomas was examined. Eighty tissue samples from 79 patients (12 premenopausal and 67 postmenopausal) were studied by a cytochemical method involving two conjugation techniques (periodate and two-stage glutaraldehyde methods) to couple 17 beta-estradiol-6-O-carboxymethyloxime-bovine serum albumin with horseradish peroxidase. Compared with the 70% (56/80) detection rate of ER by the dextran-coated charcoal method (DCCM), 80% of samples (63/80) gave a positive reaction with the cytochemical method and all of those positive with the DCCM method were positive in the cytochemical study. Only seven samples were positive by histological examination. Nuclear staining was present in four samples. One was an infiltrating lobular carcinoma with few neoplastic cells and two were intraduct carcinomas. The periodate conjugation method led to a greater degree of coupling than the two-stage glutaraldehyde method even though a higher concentration was needed to demonstrate ER with the periodate method. Careful tissue preparation and handling are necessary for obtaining good results with the cytochemical method. (19 Refs)

15. HYDROXYPROLINE AND ZINC EXCRETION IN PATIENTS WITH NEOPLASTIC BREAST DISEASE.

Percudani M, Dell'Anna B, De Lorenzis GF, Ferraccioli GF, Vaona GL
Istituto di Clinica Chirurgica 2, Universita degli Studi, Via Gramsci, 14, 43100 Parma, Italy
Int Surg; 66(3):233-236 1981

Hydroxyproline and zinc excretion were evaluated in 87 patients with neoplastic breast disease; 40 of these had carcinoma, without radiological and scintigraphy demonstration of bone metastases. In the group of patients with breast cancer, the mean values of hydroxyproline and zinc excretion were found to be significantly higher than in the group with benign breast disease: only 12 of the patients with histologically detected breast cancer had hydroxyprolinuria levels which were higher than the upper limit of the values obtained in the control group. The authors, therefore, conclude that the patients in this group must be considered as being at greater risk. (Author abstract) (12 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

16. ISOLATION AND ELECTROPHORETIC ANALYSIS OF IMMUNE COMPLEXES FROM PATIENTS WITH BREAST CANCER.

Gilead Z, Troy FA, Sulitzeanu D
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel
Eur J Cancer Clin Oncol; 17(11):1165-1176 1981

Immune complexes (IC) were isolated from sera of patients with breast cancer (BC), from effusions from patients with breast and ovarian cancer (OC) and from effusions from patients with non-malignant diseases. Isolation was carried out with the aid of tubes coated with rheumatoid factor (RF) as immunoadsorbents. The effusions were first filtered through Sephacryl S-300 columns and the large mol wt material eluted in front of the IgG peak was used as the starting material, while most of the sera were processed without prior filtration. The IC eluted from the RF-coated tubes were radioiodinated and analyzed by electrophoresis on polyacrylamide gels, followed by autoradiography. Four putative IC-derived proteins were identified in the RF eluates and designated according to their mol wt (in Kdalton): p94, p46, p17 and p13. Protein94 was found in 1/8 BC effusions, but in none of the other samples tested; 'p46', which was actually a complex of several closely spaced proteins, was identified in at least 3/16 BC sera, 6/8 BC effusions, 3/4 OC effusions and 1/5 non-malignant effusions, but in none of 17 normal sera. The upper band of the complex seemed to be present mainly, if not exclusively, in effusions from patients with neoplasia. Protein17 and p13 were found more often and in higher concentrations in the malignant effusions. All of these proteins could be precipitated by treating the RF eluates with anti human Ig serum, suggesting that they were associated with Ig, presumably as immune complexes. (Author abstract) (35 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

17. PERORAL ADMINISTRATION OF MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED CANCER OF THE BREAST. A PRELIMINARY REPORT.

Moller KA, Andersen AP
Radium Center, Municipal Hosp., DK--8000 Arhus C, Denmark
Acta Obstet Gynecol Scand [Suppl]; (101):47-48 1981

Medroxyprogesterone acetate (MPA: 500 or 1,000 mg/day) was administered po to 23 women (age 31-49 yr) with advanced breast cancer refractory to hormones and/or chemotherapy. Of the 19 patients evaluable after 2 mo of MPA therapy, 16 (84%) experienced subjective improvement (increasing appetite, increased mobility, and less pain). With 2 mo of treatment, 10 patients suffered disease progression and 3 were in a steady state. There were no complete responses, but 6 patients had a partial objective response (duration less than 4 mo to greater than 7 mo). (4 Refs)

18. A COMPARISON BETWEEN TWO POLYCHEMOTHERAPY PROTOCOLS IN THE TREATMENT OF INVASIVE BREAST CANCER.

Bianucci P, Pastorino G
VII Unita Sanitaria Locale Ligure del Savonese, Ospedale 'San Paolo' di Savona, Savona, Italy
Minerva Med; 72(45):3013-3017 1981

Seventy seven women (40-70 yr old) with invasive and metastasizing mammary cancer were studied. Because of their physiological status or due to surgery all patients were at menopause. Forty eight patients (Group A) were given chemotherapy according to protocol VAMC: 1 mg/square meter (m2) vincristine iv on day 1 and 2; 30 mg/m2 adriamycin iv on day 3; 30 mg/m2 methotrexate (M) iv on day 4, and 300 mg/m2 cyclophosphamide (C) iv on day 5. After 3 wk pause, the cycle was repeated up to 8x total. Group B 29 patients received protocol CMF: 100 mg/m2 C po daily from day 1 to 14, 40 mg/m2 M iv on day 1 and 8, and 600 mg/m2 5-fluorouracil iv on day 1 and 8. After 14 days pause, the cycle was repeated up to 12x total. The remission (partial and total) was 81,25% for patients treated with VAMC and 55.18% for those treated with CMF. Survival time after 48 mo was 47.91% for Group A and 31.03% for Group B. The subjective and objective side effects were lower in Group A. In all respects VAMC protocol gave better and more satisfactory results. (12 Refs) (In ITA)

19. TAMOXIFEN VERSUS AMINOGLUTETHIMIDE IN ADVANCED BREAST CARCINOMA: A RANDOMISED CROSS-OVER TRIAL.

Smith IE, Harris AL, Morgan M, Ford HT, Gazet JC, Harmer CL, White H, Parsons CA, Villardo A, Walsh G, McKinna JA
Breast Unit, Royal Marsden Hosp., London SW3 6JJ, England
Br Med J; 283(6304):1432-1434 1981

Altogether 117 patients with advanced breast cancer were treated with either tamoxifen 10 mg by mouth bid or aminoglutethimide 250 mg by mouth 4x daily with hydrocortisone 20 mg bid in a randomized cross-over trial in which patients who failed to respond to the first treatment or relapsed while receiving it were switched to the other. Eighteen (30%) out of 60 patients initially treated with tamoxifen achieved an objective response and 11 (18%) showed stable disease. Seventeen (30%) out of 57 patients treated initially with aminoglutethimide achieved an objective response and 13 (23%) achieved stable disease. Objective responses in bone metastases were achieved more commonly with aminoglutethimide (11 patients (35%)) than with tamoxifen (5 (17%)). The predicted median duration of response for tamoxifen was 15 mo and for aminoglutethimide over 15 mo (no significant difference). Five (15%) out of 34 patients who failed to respond to tamoxifen and four out of six patients who relapsed after responding to tamoxifen subsequently responded to aminoglutethimide. In contrast, only 2 (6%) out of 31 patients who failed to respond to aminoglutethimide and none out of four patients who relapsed while receiving aminoglutethimide subsequently responded to tamoxifen. The main side effects occurring in the 97 patients who received aminoglutethimide as first- or second-line treatment were lethargy and drowsiness (36 patients) and rash (29); seven patients had to stop treatment because of side effects. In contrast, side effects were rare and mild with tamoxifen and no patient had to stop treatment because of them. Both tamoxifen and aminoglutethimide appear from this study to be equally effective in the medical endocrine treatment of advanced breast cancer. (Author abstract) (8 Refs)

20. PRESENT AND FUTURE OF HORMONAL THERAPY IN METASTASIZED MAMMARY CARCINOMA.

Secreto G, Oriana S
Laboratorio di Ricerche Ormonali, Istituto Nazionale Tumori, Milano, Italy
Radiol Med (Torino); 67(11):867-870 1981

The androgenic activity was studied before ovariectomy in 133 patients (30-69 yr old; 17 in menopause) with advanced metastatic mammary carcinoma. In 18 normal women, av urinary excretion (ug/24 hr) of testosterone (Te) was 6.5 (0-12.7), and androstanediol (A) 35.0 (7.2-56.5). The 133 patients were divided in three groups. Group 1 had 61 patients with Te and A in the normal range. Group 2 had 46 patients with Te or A or both above normal. Group 1 and 2 were treated only by ovariectomy (OX). Twenty-six patients in Group 3 had 26 patients with excretory androgens above normal, after OX and repeated androgen determinations, were treated with dexamethasone (DXM) in repeated cycles (1.5 mg/day for 30 days) every time Te or A were above normal. Values of excretory androgens were reduced after OX, but in groups 2 and 3 they were always well above normal values. Bone metastases (Me) were prevalent in groups 2 and 3, while those in group 1 had Me mostly in viscera and soft tissue. Histological examination of resected ovaries was performed in 59 cases and in 40 hyperplasia was present. Remissions after OX were observed in 16 cases (26%) of group 1, and 25 (54.3%) of group 2. Highest response was seen in group 3, 24/26 (92%); 12 in this group showed improvement before DXM treatment. Av remission time was shortest for group 1, and longest for group 3. One patient in group 1 was in remission after 39 mo, 5 in group 2 after 12-84 mo, and 8 in group 3 after 17-94 mo. The excretory urinary androgens can indicate response to OX and usefulness of DXM treatment. (5 Refs) (In ITA)

21. TREATMENT OF STAGE I AND II ADENOCARCINOMA OF THE BREAST BY TUMOR EXCISION AND IRRADIATION.

Bedwinek J
Div. Radiation Oncology, Mallinckrodt Inst. Radiology, 4511 Forest Park, St. Louis, MO, 63108
Int J Radiat Oncol Biol Phys; 7(11):1553-1559 1981

In recent yr, the use of irradiation and breast conserving surgery as primary treatment for Stage I and II adenocarcinoma of the breast has been recommended in a number of articles. Radiation oncologists should try to participate in one of the two prospective trials evaluating the alternatives to mastectomy that are currently underway in the United States. One trial is by NCI, the other by the National Surgical Adjuvant Breast Project. If a patient cannot be entered into one of these trials or refuses to participate, her management should be based on considerations of patient selection, types of breast conserving surgical procedures, and the technical details of irradiating the intact brest, each a factor involved in the selection of patients for breast-conserving surgery and irradiation. Patient selection is discussed with respect to tumor size, breast size, multiple breast masses, distant metastases, and patient attitude. Breast conserving surgery may involve wedge resection, segmental mastectomy, or partial mastectomy (all synonymous); or tylectomy, tumorectomy, and lumpectomy (synonymous). Better cosmetic results are obtained with tylectomy. In addition to tumor excision, most patients should have either an axillary node sampling or an axillary node dissection. The question of whether to perform a low axillary node sampling or a full axillary node dissection is unresolved. Crucial technical considerations that apply to all irradiation situations include fields to be irradiated, dose, boost to the site of tumor excision, wedges or compensating filters, bolus, matching the supraclavicular field with the tangential fields, alignment of the tangential beam with the chest wall contour, and matching the tangential field with the internal mammary field. (14 Refs)

22. PRIMARY RADIATION THERAPY FOR EARLY BREAST CANCER: THE EXPERIENCE AT THE JOINT CENTER FOR RADIATION THERAPY.

Harris JR, Botnick L, Bloomer WD, Chaffey JT, Hellman S
Dept. Radiation Therapy, Joint Center Radiation Therapy, Harvard Medical Sch., 50 Binney St., Boston, MA, 02215
Int J Radiat Oncol Biol Phys; 7(11):1549-1552 1981

The results of primary radiation therapy in 176 consecutive patients with clinical Stage I and II carcinoma of the breast were reviewed (184 tumors were involved). Median follow-up was 47 mo. Fifteen of 184 cancers (8%) relapsed in the breast of axilla: 12 in the breast alone, 2 in the axilla alone, and 1 in both breast and axilla. Breast relapse was not related to the size of the primary, but was related to the presence of clinically positive axillary nodes: 7/138 (5%) with clinically negative nodes relapsed in the breast, while 6/46 (13%) with clinically positive axillary nodes relapsed. Patients undergoing interstitial implantation had a lower breast relapse rate than those not undergoing implantation: 1/73 (1%) implanted patients relapsed compared with 12/111 (11%) not implanted. Of those undergoing excisional biopsy, 1/63 (2%) implanted patients relapsed compared with 9/103 (9%) patients not implanted. Patients who received higher radiation doses had fewer relapses than those with lower doses: 8/68 (12%) who received less than 1,600 ret (rad-equivalent therapeutic) relapsed in the primary tumor area, compared to 0/19 who received more than 1,700 ret. These results demonstrate that a high level of local tumor control can be achieved following excisional biopsy by delivering 4,500-5,000 rad to the entire breast combined with supplemental irradiation to the primary tumor area. The use of external beam irradiation as a comedown boost to the primary tumor area is a reasonable alternative to interstitial implantation, which has significant disadvantages. (Author abstract) (17 Refs)

23. PROPHYLACTIC OOPHORECTOMY IN OPERABLE INSTANCES OF CARCINOMA OF THE BREAST.

Bryant AJ, Weir JA
Allan Blair Memorial Clinic, Regina, Saskatchewan, Canada
Surg Gynecol Obstet; 153(5):660-664 1981

In 1964, a prospective study was initiated of prophylactic oophorectomy in operable instances of carcinoma of the breast, in patients who showed evidence of ovarian activity. patients were randomized to a control group and a group treated by surgical castration. By December 1979, 359 patients were evaluable at 5 yr and 240 patients at 10 yr. The over-all results of the oophorectomy series were superior to that for those of the control group. Patients who had cancer confined to the breast showed no significant benefit from oophorectomy. when one to three axillary nodes were involved, women less than 50 yr of age were found to benefit significantly from prophylactic oophorectomy, in relapse-free status at 5 yr, and in survival and relapse-free status at 10 yr. Patients 50 yr of age and older showed no advantage from oophorectomy. It is suggested that there is a place for prophylactic oophorectomy in patients who are less than 50 yr of age with operable carcinoma of the breast and with positive axillary nodes. (Author abstract) (6 Refs)

24. THE EFFECT OF PREGNANCY ON THE PROGNOSIS OF CARCINOMA OF THE BREAST FOLLOWING RADICAL MASTECTOMY.

Harvey JC, Rosen PP, Ashikari R, Robbins GF, Kinne DW
Breast Service, Memorial Sloan-Kettering Cancer Center, New York, NY
Surg Gynecol Obstet; 153(5):723-725 1981

During the interval from 1940 to 1970, 41 patients treated for primary operable carcinoma of the breast had subsequent pregnancies. Of 27 patients with axillary nodes negative for tumor, 9 had first trimester abortions and 14 had pregnancies occur less than 2 yr following mastectomy. Fourteen patients had axillary nodes positive for tumor, 7 having first trimester abortions and 8 pregnancies having occurred within 2 yr of mastectomy. No detrimental effect of subsequent pregnancy could be demonstrated, even among patients with positive axillary nodes or among those whose pregnancies occurred less than 2 yr following mastectomy. Abortion could not be demonstrated to improve the survival rate. We conclude that pregnancy need not be avoided or terminated among those patients who are apparently free of recurrence after undergoing treatment for carcinoma of the breast. (Author abstract) (6 Refs)

25. SURVEILLANCE AND MANAGEMENT OF HEREDITARY BREAST CANCER.

Lynch HT, Albano WA, Organ CH, Schmitz GD, Lynch JF
Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE
Breast; 7(4):2-9 1981

Clinical and biological characteristics of hereditary breast cancer are discussed to aid in establishing guidelines for its effective surveillance and management. Characteristics include significant early age of onset, excess of bilaterality and/or specific tumor associations, vertical transmission, and improved survival over nonhereditary forms. Recent observations suggest that a genetic linkage exists between breast cancer susceptibility and the glutamate-pyruvate transaminase locus in breast cancer prone families. Consistently lower plasma levels of prolactin, gonadotropin, estrone, and estradiol were measured in a high risk population, although the differences were not statistically significant. Oral contraceptives may act synergistically with other risk factors such as nutritional changes, alcohol usage, and increased cigarette smoking and may be primarily operative in familial breast cancer. Surveillance techniques include family counseling, monthly breast self-examination, biannual physician breast examination, mammography every 2 yr, and immediate biopsy of all dominant nodules. Existing breast cancers should receive standard evaluation and treatment, and the contralateral breast should be evaluated by mammogram and biopsy. The control of hereditary breast cancer could be aided immeasurably by the assembly of breast cancer prone kindreds in a carefully designed study. (35 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

26. EARLY AGE AT FIRST BIRTH AND DECREASED RISK OF BREAST CANCER.

Bain C, Willett W, Rosner B, Speizer FE, Belanger C, Hennekens CH (c/o Hennekens), Channing Lab., 180 Longwood Ave., Boston, MA, 02115
Am J Epidemiol; 114(5):705-709 1981

The relationship between age at birth of a first child and breast cancer was evaluated for 1,159 affected women and 11,590 women without cancer in data collected in 1976 among married female registered nurses residing in 11 states in the United States. A positive trend of increasing risk of breast cancer with later ages at first birth was found (chi21 for trend in proportions = 30.9, p less than 0.01). Adjustment for potential confounding variables by multiple logistic regression did not affect this trend. The presence of this relationship using non-hospitalized controls of similar social status to cases supports the reality of this association, which has recently been challenged as an artifact due to inappropriate choice of hospitalized controls. (Author abstract) (22 Refs)

27. A PROSPECTIVE STUDY OF PLASMA PROLACTIN LEVELS AND SUBSEQUENT RISK OF BREAST CANCER.

Kwa HG, Cleton F, Wang DY, Bulbrook RD, Bulstrode JC, Hayward JL, Millis RR, Cuzick J
Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Plesmanlaan 121, 10066CX Amsterdam, The Netherlands
Int J Cancer; 28(6):673-676 1981

Plasma prolactin was measured in 2,572 premenopausal, 628 menopausal, and 1,666 peri- and postmenopausal women who were apparently healthy. Breast cancer was subsequently diagnosed in 47 of these women at a median time of 5 years after blood collection (pre-cancer cases). Prolactin levels in premenopausal cases increased significantly with age whereas this was not found in matched controls. The perimenopausal cases were characterized by extreme variability in prolactin levels. In post-menopausal women who developed breast cancer, the prolactin levels were significantly elevated, being at or above the 70th percentile for the controls. In this group the results are consistent with prolactin acting as a late-stage tumor promoter. (Author abstract) (18 Refs)

28. DIETARY FACTORS AND BREAST CANCER RISK.

Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF
Environmental Epidemiology Branch, NCI, Bethesda, MD
Int J Cancer; 28(6):685-689 1981

As part of a case-control study in northern Alberta, Canada, 577 women aged 30-80 with breast cancer diagnosed during 1976-77 and a population-based age-stratified random sample of 826 disease-free female controls were questioned about certain aspects of their diet. Computing relative risks (RRs) by tertiles, significant increasing trends were found with more frequent consumption of beef (RRs of 1.0, 2.3, 1.5; test for trend, p less than 0.001), pork (RRs of 1.0, 1.6, 2.2; test for trend, p less than 0.001), and sweet desserts (RRs of 1.0, 1.3, 1.5; test for trend, p = 0.01). Elevated risks were also noted for use of butter at the table and for frying with butter or margarine, as opposed to vegetable oils. The association of total beef and pork consumption with breast cancer was not materially affected by controlling for age at first birth, family history of breast cancer, previous benign breast biopsy or socioeconomic status.

Nor was the association reduced by controlling for ages of menarche and menopause, even though within the control series the intake of beef and pork reported in adult life was higher among those with a lower age at menarche or an older age at natural menopause. (Author abstract) (26 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

29. EFFECT OF MEDROXYPROGESTERONE ACETATE AND DOXORUBICIN ON SUBLINES OF 13762 MAMMARY ADENOCARCINOMA IN RATS.

Formelli F, Zaccheo T, Casazza AM, Bellini O, Di Marco A
Instituto Nazionale per lo Studio e la Cura Dei Tumori, Via Venezian, 1, 20133 Milan, Italy
Eur J Cancer Clin Oncol; 17(11):1211-1221 1981

The 13762 mammary adenocarcinoma was subjected to serial transplantation in rats, freezing and thawing and in vitro cultivation. Following these procedures, various sublines were identified which differed in histological pattern, oncogenicity and sensitivity to medroxyprogesterone acetate treatment. Medroxyprogesterone acetate, administered sc at the dose of 100 mg/kg/day, 5 days/wk for 4 wk, delayed tumor onset and growth of sublines that had maintained their sensitivity to 17-beta-estradiol. Doxorubicin, administered iv at the dose of 3.6 mg/kg once a wk for 4 wk, was more active on the hormone-sensitive than on the hormone-insensitive subline. Simultaneous combined treatment for 4 wk with these agents caused higher growth inhibition than either single agent given alone. Other schedules of treatment were less effective. The following conclusions can be drawn: (1) the 13762 mammary tumor is heterogeneous, and hormone-sensitive or insensitive cell populations can be selected by simple manipulations; (2) there is no correlation between histological pattern and hormone sensitivity; (3) medroxyprogesterone acetate is active on sublines sensitive to 17-beta-estradiol treatment, but it also improves the activity of doxorubicin on hormone-insensitive sublines. (Author abstract) (22 Refs)

30. METABOLIC MODIFICATION BY INSULIN ENHANCES METHOTREXATE CYTOTOXICITY IN MCF-7 HUMAN BREAST CANCER CELLS.

Alabaster O, Vonderhaar BK, Shafie SM
Dept. Medicine, George Washington Univ., Suite 625, 2150 Pennsylvania Ave., N.W., Washington, DC, 20037
Eur J Cancer Clin Oncol; 17(11):1223-1228 1981

Insulin, which activates and modifies metabolic pathways in MCF-7 human breast cancer cells, is shown to increase the cytotoxic effect of methotrexate up to 10,000-fold in vitro. This enhanced cytotoxicity is not due to an increased bound intracellular drug level, an increased growth rate or an increase in S phase cells, but may involve the modification or activation of biochemical pathways associated with cell growth, even in cells not undergoing DNA synthesis. This observation supports the hypothesis that tumor cell sensitivity to chemotherapy could be increased by using agents that can activate the biochemical or metabolic pathways that determine the cytotoxic process. (Author abstract) (13 Refs)

31. WHOLE-CELL UPTAKE AND NUCLEAR LOCALIZATION OF 1,25-DIHYDROXYCHOLECALCIFEROL BY BREAST CANCER CELLS (T47 D) IN CULTURE.

Sher E, Eisman JA, Moseley JM, Martin TJ
(c/o Eisman) Univ. Melbourne Dept. Medicine, Repatriation General Hosp., Heidelberg, Victoria 3081, Australia
Biochem J; 200(2):315-320 1981

Specific high-affinity receptors for 1,25-dihydroxycholecalciferol [1,25-(OH)2D3] have been described recently in broken-cell preparations of several cultured human breast cancer cell lines including the T47 D line. It was necessary to determine whether intact breast cancer cells in culture would bind 1,25-(OH)2D3 specifically and whether the next step in the proposed scheme of action, ie nuclear translocation, occurred. The following results were obtained. (1) Specific uptake of 1,25-(OH)2D3 by T47 D cells occurs in intact cells in culture. (2) The rate of uptake is proportional to medium 1,25-(OH)2D3 concentration but is slow compared with that of other steroid hormones, eg, estradiol, under identical conditions. Even at 0.5 nM-1,25-(OH)2D3 in the medium, at least 4 hr are required to reach max compared with less than 1 hr for estradiol binding. (3) Estimation of binding characteristics by Scatchard analysis indicates a single class of binding sites with Kd of 68 pM and 11,800 binding sites/cell, which are similar results to those obtained with broken-cell preparations. (4) Inclusion of various vitamin D metabolites in the incubation medium decreased specific binding of 1,25-(OH)2D3 by the intact cells in a manner identical with their effects in the broken-cell preparation and with potencies similar to their potency on Ca++ transport and bone resorption in vivo. Order of potency was 1,25-(OH)2D3 greater than (24R)-1,24,25-trihydroxycholecalciferol much greater than 25-hydroxycholecalciferol greater than (25R)-24,25-dihydroxycholecalciferol much greater than (25R)-25,26-dihydroxycholecalciferol. (5) In the 1,25-(OH)2D3-depleted state, 80% of the 1,25(OH)2D3 receptor is found in the cytosol fraction of the cells even when the subcellular fractionation is performed under low-salt conditions. By contrast after incubation with [3H]1,25-(OH)2D3, 59% of the specific 1,25-(OH)2D3 binding is found in the partially purified nuclei fraction. These data indicate that nuclear translocation of the receptor-hormone complex takes place in the intact T47 D cell. The results also support the hypothesis that the 1,25-(OH)2D3 receptor is functional in this cultured breast cancer cell line, which may provide a useful model for further study of the early biochemical events in 1,25-(OH)2D3 action. (Author abstract) (31 Refs)

32. THE SPECIFIC BINDING OF ANDROGENS AND THE SUBSEQUENT DISTRIBUTION OF ANDROGEN-RECEPTOR COMPLEXES WITHIN MCF-7 HUMAN BREAST CANCER CELLS.

MacIndoe JH, Woods GR, Lee FJ
Dept. Internal Medicine, Veterans Admin. Medical Center, Iowa City, IA, 52240
Steroids; 38(4):439-452 1981

Using a whole cell suspension assay technique, we have examined both the specific binding of testosterone (T) and dihydrotestosterone (17beta-hydroxy-5alpha-androstan-3-one) (DHT) and the subsequent distribution of androgen binding activity within MCF-7 human breast cancer cells. We have observed that both androgens are bound with high affinity to the same single class of receptor which is present at a concentration of approx 8,000 sites per cell. The incubation of cells with either T or DHT was followed by the nuclear accumulation of specifically bound ligand which increased to max values within 1 hr and then decreased thereafter. However, only about 30% of the total cellular specific binding activity observed with either androgen was localized within the nuclear compartment at any time during a 4 hr incubation. Further examination of the extranuclear binding component suggested that a substantial portion of this activity was localized to the particulate fraction of the cytoplasm. The results of these studies suggest that both T and DHT are capable of exerting biological activity within MCF-7 cells, and raise the interesting possibility that androgen-receptor complexes may participate in the direct regulation of mitochondrial and/or microsomal function in this system. (Author abstract) (15 Refs)

33. EFFECTS OF ESTROGENS AND ANTIESTROGENS ON ESTROGEN RECEPTOR DYNAMICS AND THE INDUCTION OF PROGESTERONE RECEPTOR IN MCF-7 HUMAN BREAST CANCER CELLS.

Eckert RL, Katzenellenbogen BS
(c/o Katzenellenbogen) Sch. Basic Medical Sciences, Univ. Illinois Coll. Medicin e, Urbana, IL, 61801
Cancer Res; 42(1):139-144 1982

Antiestrogens appear to be useful in the treatment of endocrine-responsive breast cancers in humans. We have examined the effects of estrogens (estradiol and diethylstilbestrol), and antiestrogens with a range of affinities for estrogen receptor (ER), on intracellular ER dynamics and biological response (progesterone receptor) induction in MCF-7 human breast cancer cells. The triphenylethylene antiestrogens studied are alpha- *p-[2-(1-pyrrolidino)ethoxy]phenyl* -4-methoxy alpha'-nitrostilbene (Cl628), alpha- *p-[2-(1pyrrolidino)ethoxy]phenyl* -4-hydroxy alpha'-nitrostilbene, cis- *3-[p-(1,2,3,4,-tetrahydro-6-methoxy-2-phenyl-1 naphthyl)phenoxy]-1,2-propanediol* , and cis-*3-[p-(1,2,3,4-tetrahydro-6-hydroxy-2-phenyl-1 naphthyl)phenoxy]-1,2,propanediol. The results indicate that: (a) ER translocation to the nucleus and progesterone receptor induction appear to be related to ligand affinity; (b) antiestrogens can differ substantially from one another in their dynamics of interaction with ER and in their abilities to stimulate increases in cellular progesterone receptor; (c) processing of ER by antiestrogens such as C1628 does not ensure subsequent induction of progesterone receptor; and (d) an apparently complex relationship exists between the presence and duration of hormone receptor complexes in the nucleus and the induction of progesterone receptor in MCF-7 cells. Since all four antiestrogens inhibit MCF-7 cell growth but differ in their ability to increase cellular progesterone receptor levels, these studies indicate that growth and progesterone receptor induction are phenomena that are independently modulated by antiestrogens in these human breast cancer cells. (36 Refs)*

34. CLONAL GROWTH OF NORMAL AND MALIGNANT HUMAN BREAST EPITHELIA.

Lan S, Smith HS, Stampfer MR
Dept. Surgery, Hosp. Albert Eistein Coll. Medicine, 1825 Eastchester Road, Bronx, NY, 10461
J Surg Oncol; 18(3):317-322 1981

We have developed an efficient method for the growth of colonies from single breast epithelial cells derived from nonmalignant, primary, and metastatic surgical specimens. The immediate sources of the cells were primary and secondry mass cultures. An enriched culture medium and fibroblast feeder layers were used. A linear relationship between the number of cells cultured and the number of colonies obtained was found. Efficiency of colony formation was higher for those derived from nonmalignant specimens (mean 24%) than those derived from malignant specimens (mean 11%). Fibroblast feeder layers increased the efficiency of colony formation and also supported extended growth of colonies. (Author abstract) (14 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abele JS 7
Alabaster O 30
Albanò WA 25
Andersen AP 17
Andersson I 3
Ashikari R 24
Bain C 26
Bedwinek J 21
Belanger C 26
Bellini O 29
Bianucci P 18
Bishop H 11
Bloomer WD 22
Blot WJ 28
Bodin JP 2
Bolla M 2
Botnick L 22
Bryant AJ 23
Bulbrook RD 27
Bulstrode JC 27
Burns PE 28
Camiolo SM 12
Campbell C 11
Carpentier E 2
Casazza AM 29
Castiglione V 4
Cecco L 13
Cerra M 13
Chaffey JT 22
Cleton F 27
Cohen AM 5
Comet M 2
Cunsolc A 6
Cuzick J 27
D'Antona A 4
Daniel P 11
Davis JC 9
De Lorenzis GF 15
Dean PB 8
Dell'Anna B 15
Dellafiore L 4
Di Marco A 29
Duncan JN 9
Dupre A 2
Eckert RL 33
Eisman JA 31
Elwood JM 10
Evers JL 12
Ferraccioli GF 15
Ferrario L 4
Ford HT 19
Formelli F 29
Fraumeni JF 28
Gabelle P 2
Gaskell SJ 11
Gazet JC 19
Gilead Z 16
Godolphin W 10
Hamilton B 1
Harmer CL 19
Harris AL 19
Harris JR 22
Harvey JC 24
Hayward JL 27
Hellman S 22
Hennekens CH 26
Hobika GH 12
Karpman HL 1
Katzenellenboge 33
Kinne DW 24
Kopans DB 5
Kwa HG 27
Lan S 34
Lee FJ 32
Lees AW 28
Lubin JH 28
Luzzatti G 4
Lynch HT 25
Lynch JF 25
MacIndoe JH 32
Madeja JM 12
Maldarizzi F 6
Markus G 12
Martin TJ 31
McKinna JA 19
Meyer JE 5
Millis RR 27
Moller KA 17
Morgan M 19
Mortara G 4
Moseley JM 31
Nicholson RI 11
Organ CH 25
Oriana S 20
Parsons CA 19
Pastorino G 18
Patel J 12
Pentek Z 8
Percudani M 15
Pizzinelli P 4
Robbins GF 24
Romano M 13
Rosen PP 24
Rosner B 26
Scandellari S 6
Schmitz GD 25
Schneider SL 12
Secreto G 20
Shafie SM 30
Sher E 31
Sickles EA 7
Smith HS 34
Smith JE 19
Speizer FE 26
Spinelli JJ 10
Stampfer MR 34
Sulitzeanu D 16
Swiercz P 2
Tabar L 8
Troy FA 16
Vaona GL 15
Vecchi R 6
Villardo A 19
Vitali T 4
Vitolo A 6
Vonderhaar BK 30
Wade AP 9
Walker RA 14
Walker S 9
Walsh G 19
Wang DY 27
Weir JA 23
White H 19
Willett W 26
Wood WC 5
Woods GR 32
Zaccheo T 29
Zanni E 6
Ziegler RG 28

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)........ 1
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS........ 2-6
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS........ 7-16
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS........ 17-19
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)........ 20-41
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY........ 42-43
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)........ 44-48

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE 20. 3173/2:

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. DETECTION OF EARLY FORMS OF BREAST CANCER BY MASS SCREENING EXAMINATIONS.

Pavlov KA, Semiglazov VF
Prof. N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, 188646 Leningrad, USSR
Neoplasma; 28(5):611-615 1981

Data are presented on the results of the complex prophylactic examinations of women at Prof. Petrov Research Institute of Oncology of the USSR Ministry of Health for the period 1976-1980. Four annual prophylactic examinations (clinical method, thermography, mammography, biopsy) of 4,823 women over 35 years of age revealed breast cancer in 51 persons (ie in 1.05% of the examined women). In 52.9% of cases tumors were revealed by clinical examination + mammography, in 29.4% by mammography alone, in 17.5% by clinical examination alone. In 38 out of 51 breast cancer patients (i.e. in 74.5% of cases) the detected tumors were less than 2 cm in diameter (stage I, 'minimal' and preinvasive carcinomas). (Author abstract) (8 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. HOW REPRESENTATIVE IS A LYMPH NODE BIOPSY FROM THE AXILLA IN A NODE-NEGATIVE BREAST CANCER PATIENT?

Hartveit F
Dept. Pathology, Haukeland Hosp., 5016 Bergen, Norway
Clin Oncol; 7(4):303-309 1981

The histology is reported in all lymph nodes (617) recovered from the axillary dissection specimens from 40 women with node-negative breast cancer. About 40% more nodes were recovered following clearing of the specimens with cedar wood oil. Half of them were under 3 mm in diameter, and many were thus unsuitable for histological evaluation of the lymphoid tissue response. Marked reactions were identified from study of the four largest nodes present, but the less pronounced were missed. These four nodes were recovered before clearing in 86% of cases. The degree of variation from node to node differed with the factors studied, but was in general considerable. Evaluation of the nodal response on the basis of a random sample, as that obtained on nodal biopsy, cannot be expected to give a reliable guide to the lympho-proliferative response in patients of this type. (Author abstract) (7 Refs)

3. RADIOGRAPHIC EVALUATION OF THERAPEUTIC RESPONSE IN BONY METASTASES OF BREAST CANCER.

Libshitz HI, Hortobagyi GN
Dept. Diagnostic Radiology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Skeletal Radiol; 7(3):159-165 1981

Radiographic appearance of response to chemotherapy was investigated in 50 previously untreated breast cancer patients (29-69 yr old) with known metastases in bone. Chemotherapy programs consisted of 5-fluorouracil, adriamycin, cyclophosphamide and methotrexate, or equivalents. Pretreatment evaluation of radiographs revealed osseous metastases in 44 classified as follows: lytic (26),, mixed (11), blastic (4), and fracture (3). Lytic metastases showed response in a definite sequence: sclerotic rim, filling in, uniformly blastic, and uniform fading. Disease progression was indicated by increase in the size of lytic areas or destruction in previously responding areas. Mixed lesions initially show a rim of sclerosis. Further response is similar to lytic lesions. Healing in blastic lesions, while difficult to evaluate, was indicated by fading of the blastic response to a normal bony density and trabecular pattern. Disease progression was indicated by increasing areas of blastic change or the development of destruction within a blastic lesion. Sixteen of 26 patients with lytic metastases showed no response, stayed stable less than 12 mo, or responded less than 12 mo to chemotherapy. Ten patients remained stable or responded greater than 12 mo. Twelve of 15 patients with mixed or blastic metastases responded to therapy of 12 mo or longer. Evaluation of metastases in bone should include bone scan, radiographs, and clinical history. (15 Refs)

4. THE ROLE OF MAMMOGRAPHY IN EVALUATING PATIENTS WITH EARLY CARCINOMA OF THE BREAST FOR TYLECTOMY AND RADIATION THERAPY.

Gefter WB, Friedman AK, Goodman RL
Dept. Radiology, Hosp. Univ. Pennsylvania, 3400 Spruce St., Philadelphia, PA, 19104
Radiology; 142(1):77-80 1982

The value of mammography in treatment planning for early breast cancer following excisional biopsy was studied in 38 patients. One-third of the post-biopsy mammograms yielded information useful for therapy or follow-up, specifically the presence or absence of gross residual tumor [11] and detection of occult lesions in the opposite breast or axillary nodes [3]. They also proved valuable as base-line studies, since scars seen on post-therapy mammograms may simulate new or recurrent tumor [3]. Approx half [21] of the post-biopsy studies were nondiagnostic because of dense parenchyma [14] or biopsy-related distortion [7]. Four were considered falsely positive for residual tumor. These results indicate that mammography can contribute significantly to the management of patients undergoing tylectomy and primary radiotherapy for breast cancer. (Author abstract) (21 Refs)

5. MAMMOGRAPHIC PARENCHYMAL PATTERNS: RISK INDICATOR FOR BREAST CANCER?

Tabar L, Dean PB
Dept. Mammography, Falun Central Hosp., 791 82 Falun, Sweden
JAMA; 247(2):185-189 1982

Mammographic parenchymal patterns, originally presented as a new risk factor for breast cancer, have been prospectively studied in a large (27,157 examinations) consecutive screening population. Although there is a significantly higher risk of breast cancer in the so-called dysplastic breasts (P2 and DY pattern groups), the classification is of little practical value, as more than 72% of the cancers in the prevalent population were found in the so-called low-risk breasts (N1 and P1 pattern groups). A similar trend occurred at repeated screening of younger women, in which most of the 'incident' cancers were found in the 'low-risk' breasts. These patterns should not be used to influence patient management or screening programs. (Author abstract) (20 Refs)

6. CORRELATION OF ELASTOSIS WITH PROGNOSTIC INDICATORS IN HUMAN BREAST CARCINOMA (MEETING ABSTRACT).

Bowen JH, Mossler JA, McCarty KJ
Department of Pathology, Duke University Medical Center, Durham, NC, 27710
Am J Clin Pathol; 76(3):352 1981

Histochemically demonstrable elastosis in human breast carcinoma has been suggested to represent a potentially useful prognostic indicator. The parameters of histologic grade and sex steroid receptor content are known indicators of tumor differentiation. In this study elastosis, estrogen (ER), and progesterone (PR) receptor content and histologic grade were evaluated in 74 primary breast carcinomas. Elastosis was evaluated by a Verhoeff-Van Gieson stain and categorized as 0, 1, 2, or 3+. ER and PR content were determined by dextran coated charcoal and/or sucrose density gradient analyses. Elastosis grades 2-3 correlated with ER greater than 10 fm/mg protein. Elastosis and PR did not show a significant correlation; however, when ER and PR were simultaneously compared to elastosis, 47.9% of tumors with elastosis grades 0-1 were ER+PR- or ER-PR+ while such discordance of ER and PR was found in only 12.0% of tumors with grades 2-3 elastosis. In histologic grade I tumors, 64.7% had elastosis grades 2-3 as compared with 29.8% among histologic grade II and III tumors. These findings suggest that elastosis is associated with differentiation as manifested by histologic grade or receptor content and may have significant implications in the prognosis of breast cancer. (no Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

7. THE SIGNIFICANCE OF TUMOR MARKER ASSAY IN THE STAGING OF BREAST CANCER. ASSESSMENT OF FERRITIN AND BETA-HCG LEVELS.

Micali B, Gioffre Florio MA, Venuti A, Giorgianni G, Saitta FP
Istituto di I Patologia Chirurgica, Policlinico Universitario Gazzi, 98100 Messina, Italy
J Nucl Med Allied Sci; 25(3):65-70 1981

The relationship between the clinical stage of breast cancer and serum levels of ferritin and beta-human chorionic gonadotropin (b-HCG) was studied in 45 post-menopausal patients. Serum ferritin (nanog/ml) levels in patients with regional lymph node involvement were significantly greater than those in the patients without node involvement (102.17 +-27.0 vs 51.53 +-17.2). Ferritin levels showed progressive increase in the patients with metastatic disease, compared with M0 patients. Tumor size was not related to serum ferritin levels. The b-HCG levels was not related to the clinical TNM stage of breast cancer. (14 Refs)

8. MAINTENANCE OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER.

Ben-David M, Dror Y, Biran S
Dept. Pharmacology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91010 Jerusalem, Israel
Isr J Med Sci; 17(9/10):965-969 1981

Breast tissue specimens of 110 women with various stages of breast cancer were tested in vitro to determine their specific binding sites for human prolactin. In contrast to the case of steroid receptors, binding sites for prolactin were found in the vast majority of breast cancer tissue. Distribution profiles giving amount of prolactin receptor and their affinity coefficients were found to be similar in the tissues of women whose ages, hormonal status, or stage of breast cancer varied. These findings show that in contrast to steroid receptors, human breast cancer tissue maintains binding sites for prolactin. The findings also indicate that there may be a higher dependency of breast cancer on prolactin than on steroids. Clinical trials must be carried out to determine the role of 'positive' prolactin receptors in prognosis and prediction of response to future hormone therapy. (Author abstract) (20 Refs)

9. HISTOCHEMICAL DEMONSTRATION OF ESTROGEN RECEPTORS IN BREAST CANCER.

Paulsen SM, Johansen P, Rasmussen KS, Mygind H
Patologisk institut, Aalborg sygehus Nord, DK-9000 Aalborg, Denmark
Ugeskr Laeger; 143(47):3119-3123 1981

Histochemical method for the detection of estrogen receptors (ERs) in breast carcinoma tissue is described, and results obtained by this method in tissue specimens from 46 breast cancer patients are reported. The histochemical detection of ERs is based on counting of fluorescent (positive) cells after incubation with fluorescein isothiocyanate-conjugated 17-beta-estradiol. ER+ carcinomas were defined as those containing more than 10% fluorescent cells, which was found consistent with the biochemical criterion of ER+ breast carcinoma (greater than 10 femtomoles/mg protein). The patients included 14 premenopausal and climacteric patients (Group I) and 32 patients in the menopause (Group II). The frequencies of ER+ carcinomas were 8/14 in Group I and 24/32 in Group II. The frequencies of ER+ carcinomas were 25/38 for infiltrating ductal carcinomas, 6/7 for infiltrating lobular carcinomas, and 1/1 for colloid carcinoma. Even though the relationship between the histochemically and biochemically demonstrated ERs is not fully elucidated, the histochemical method is able to supplement the biochemical method. (15 Refs) (In DAN)

10. THE PRESENCE OF A SECOND, SPECIFIC ESTROGEN BINDING SITE IN HUMAN BREAST CANCER.

Panko WB, Watson CS, Clark JH
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 14(12):1311-1316 1981

Type II estrogen binding site (II EBS) was analyzed in human breast tumor specimens. Saturation analysis of cytosol derived from pooled tumor specimens was conducted over the 3H-estradiol (3H-ES) concentration range 0.5-120 nanoM (nM). Scatchard plotting of saturation data revealed the presence of a two-component binding system. The type I site, believed to be cytoplasmic estrogen receptor (ER), displayed an affinity and concentration compatible with the ER system. The type II site had a markedly lower affinity for 3H-ES and significantly higher concentration. A similar two-component Scatchard plot was obtained when moxestrol was used with a different pool of tumor tissue. The post-labeled sucrose gradient method was used with cytosol derived from pooled tumor tissue. If cytosol was pre-labeled with 40 nM 3H-ES, the specific binding at both the 8S and 4S regions of the gradient showed some augmentation. However, if the cytosol was post-labeled, marked augmentation of specific binding in the 4S region of the gradient occurred. Tumors of the colon (2), lung (2), and muscle (1) were subjected to pre- and post-labeled sucrose gradient analysis with 40 nM 3H-ES. The difference between specific binding in the 4S region of the pre-labeled (2 nM) and the post-labeled (40 nM) gradient was defined as the amount of type II EBS in the tumor. Neither ER nor type II EBS were detected in any of the five tumors. When the concentration of type II EBS was correlated with the concentration of ER, a very strong positive correlation was noted. The results indicated that breast cancer cytosol contains a specific, secondary estrogen binding site. (16 Refs)

11. PROSTAGLANDIN E2 AND CYCLIC AMP IN TUMOR AND PLASMA OF BREAST CANCER PATIENTS.

Malachi T, Chaimoff C, Feller N, Halbrecht I
(c/o Halbrecht) B. Gattegno Res. Inst., Hasharon Hosp., Petah-Tikva, Israel
J Cancer Res Clin Oncol; 102(1):71-79 1981

Prostaglandin E2 and cyclic AMP (cAMP) levels were measured in tumors and plasma of 78 patients with benign and malignant breast tumors. Two groups of malignant tissues were found, one with a high level of PGE2 (M = 55.4 pg/mg) and one with a low level (M = 10.7 pg/mg). The low level did not differ significantly from the benign tissue level (M = 8.7 pg/mg). Two malignant groups could not be detected in the plasma levels. Plasma PGE2 concentration (in form of the 13,14-dihydro-15-Keto metabolite) did not reflect the tissue levels, and no difference was found between the benign (M = 59.9 pg/ml) and the malignant (M = 62.3 pg/ml) patients, but both concentrations were higher than those of healthy controls (M = 34.4 pg/ml). The stage of the cancer, the histological classification and, most important, the period of survival, could not be related to the differences in the PGE2 tissue levels. Neither could plasma cAMP be nominated as a breast cancer marker because no difference was found between the cAMP levels of benign tumor patients (M = 16.48 pmol/ml), of malignant tumor patients (M = 21.24 pmol/ml) and of healthy controls (M = 19.07 pmol/ml). The conclusion is that although high amounts of PGE2 appear in some malignant breast tumors, they do not affect the clinical situation. These results may explain the failure to treat human breast cancer patients with prostaglandin synthetase inhibitors. (Author abstract) (28 Refs)

12. COMPARISON OF STEROID RECEPTOR CONTENT AND DNA LEVELS IN HUMAN BREAST CANCERS (MEETING ABSTRACT).

Thornthwaite JT, Coulson PB
Departments of Biophysics and Physiology, Quillen-Dishner College of Medicine, East Tennessee State University, Johnson City, TN, 37614
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Slona-Kettering Cancer Center; 1981

The purpose of this study was to determine if there is any correlation between the degree of heteroploidy in human breast cancers and the quantity of steroid receptors in these tissues. Frozen specimens (-85 C) with estrogen cytosolic receptor levels between 0-502 fm/mg cytosolic protein were prepared for DNA flow cytometric analysis. This was accomplished by mincing the tissues in a special nuclear isolation medium (NIM) containing 10 ug/ml of 4',6-diamindino-2 phenylindole-2HCl (DAPI) at room temperature. The isolated nuclei were filtered (70 micron mesh) and syringed to assure a monodispersed nuclear population. A modified PHYWE ICP-21 flow cytometer, either with the PHYWE flow chamber for DNA or the Cell Technology transducer for dual parameter analysis (electronic nuclear vol vs DNA fluorescence) was utilized. The range of CVs of the G1/0 peaks of NIM-DAPI prepared tissues were routinely 1-3%. Samples were grouped according to their DNA contents and designated diploid-like, diploid/hypodiploid, diploid/hyperdiploid, diploid/multiploid, or diploid/hypertetraploid. No correlation could be seen between the percentage of hyperdiploid cells or the proliferation index compared to the estrogen (3H-estradiol), progesteron (3H-R5020) or, testosterone (3H-R1881) receptor levels. In 84 tumors, the percentage of breast cancers which were diploid or aneuploid were 30% or 70%, respectively. Work is in progress to see if there is any correlation between the degree of aneuploidy and recurrence. (no Refs)

13. ESTROGEN RECEPTOR CYTOCHEMISTRY IN HUMAN BREAST CANCER: STATUS AND PROSPECTS.

Nenci I
Istituto Anatomia Patologica, Universita di Ferrara, Ferrara 44100, Italy
Cancer; 48(12):2674-2686 1981

Advances in knowledge of the endocrine control of neoplastic growth can be expected to stem directly from advances in pertinent techniques. Following this theme, the present paper describes how recent development in cytochemical techniques for estrogen receptors may maintain this expectation and lead to significant progress in the basic knowledge of breast cancer that can influence the treatment approach. Cytochemical techniques have shown that the binding of estrogen to target cells and tissues can be specifically visualized: moreover, estrogen binding sites characterized cytochemically under controlled conditions have proved to fulfill the accepted criteria for estrogen receptors. Some working solutions to basic questi ons concerning the tumor hormone-responsiveness have been provided and more precise explanations of fundamental growth-regulatory mechanisms are expected to emerge from the approach to breast cancer by cytologic endocrinology. However, in the present state of the art and in spite of tantalizing bits of data, cytochemical techniques for estrogen receptors do not seem extensible to routine purposes, as alternative to biochemical receptor assays in selecting patients for endocrine therapy. One must have strong reservations on their clinical use because of the almost complete lack of information about correlations of cytochemical results with the response to endocrine therapy. More studies evaluating the practical validity of estrogen receptor cytochemistry are required. (Author abstract) (92 Refs)

14. SUPPRESSOR CELL ACTIVITY OF FERRITIN-BEARING LYMPHOCYTES IN PATIENTS WITH BREAST CANCER.

Moroz C, Kupfer B
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, 49100 Petah Tikva, Israel
Isr J Med Sci; 17(9/10):879-881 1981

In patients with early stages (I, II) of breast cancer we identified a subset of circulating lymphocytes that carry ferritin on their surface. No such lymphocytes were identified in normal women nor in women with benign breast disease. These cells did not form spontaneous rosettes with sheep red blood cells. Further studies revealed that in vitro treatment of the patients' lymphocytes with levamisole resulted in the removal of the surface ferritin and in an increase in the reactivity of the lymphocytes in mixed lymphocyte culture (MLC). Separation of the ferritin-positive lymphocytes from the E-rosetting T cells resulted in an increased reactivity of the patients' T cells in MLC. Readdition of the fraction containing the ferritin-positive cells to a mixed lymphocyte culture resulted in a decrease in the proliferative response of the patients' T lymphocytes. It is suggested that the ferritin-positive lymphocytes in breast cancer patients represent an active suppressor cell subset. (Author abstract) (13 Refs)

15. A COMPARISON OF GAMMA GLUTAMYL TRANSPEPTIDASE ACTIVITY IN BENIGN HUMAN MAMMARY LESIONS AND PRIMARY, RECURRENT AND METASTATIC BREAST CARCINOMA (MEETING ABSTRACT).

Levine SE, McCarty KS, McCarty KS, Michalopoulos GK
Departments of Pathology, Duke University Medical Center, Durham, NC, 27710
Am J Clin Pathol; 76(3):354 1981

Gamma glutamyl transpeptidase (GGT) has been suggested to respresent an 'oncofetal marker' in liver and skin neoplasia. This enzyme is histochemically demonstrable in human breast cipthelium. A characteristic pattern of luminal and apical GGT activity greater than non-apical (homogeneous) cytoplasmic staining is seen in benign breast tissue (23 benign and dysplastic breast lesions). Malignant breast tumors (91 primary and 17 metastatic) exhibit a bimodal distribution of GGT staining intensity ranging from markedly increased to absent cytoplasmic staining. Metastatic breast tumors exhibited a GGT activity curve skewed toward high GGT scores when compared to the bimodal GGT activity curve for primary tumors. Although the GGT activity of the tumors was independent of estrogen-progesterone receptor content, the GGT activity of a tumor appears to complement the tumor's estrogen and progesterone receptor content as a prognostic indicator of tumor behavior. Shifts in GGT staining from the characteristic benign pattern to weak or intense homogeneous cytoplasmic histochemical activity are observed in 'pre-malignant' or 'borderline' lesions. (no Refs)

16. MEASUREMENTS OF DNA SYNTHESIS AND ESTROGEN RECEPTOR IN NEEDLE ASPIRATES AS POWERFUL METHODS IN THE MANAGEMENT OF MAMMARY CARCINOMA.

Nordenskjold B, Skoog L, Wallgren A, Silfversward C, Gustafsson S, Ljung BM, Westerberg H, Gustafsson JA, Wrange O
Karolinska Hosp., Karolinska Inst. and Univ. Linkoping, Linkoping, Sweden
Adv Enzyme Regul; 19:489-496 1981

Techniques used in management of mammary carcinoma (MC) are presented. Monitoring biochemical parameters in small tissue samples from needle aspirates is of value. Measurement of estradiol receptor (ER) in MC is based on the electrofocusing of 3H-estradiol bound receptor in slices of polyacrylamide gel. ER level in the tumor correlates with pathological type of MC. Medullary carcinoma and comedocarcinomas are receptor poor; papillary carcinomas are receptor rich. Measurements of ER and DNA in needle aspirates from primary or recurrent carcinoma correlate significantly. Primary MC from 50 patients were characterized by 3H-thymidine incorporation and ER analysis of needle aspirates. Results correlating with pathological analysis showed that ductal carcinomas of a low degree of differentiation have a decreased mean receptor value. Decreased DNA synthesis can be registered 1-3 wk after initiation of endocrine therapy, before a significant reduction in tumor diameters can be noted. (13 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

17. MAXIMIZING DIFFERENCES IN THE CONCANAVALIN A-INDUCED BLASTOGENIC RESPONSES OF LYMPHOCYTES FROM BREAST CANCER PATIENTS AND CONTROLS BY THE USE OF ALPHA-METHYL-D-MANNOSIDE.

Distasio JA, Cheresh DA, Schilder RJ, Vogel CL, Silverman MA, Lopez DM
Dept. Microbiology D4-4, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
JNCI; 68(1):69-74 1982

In an attempt to magnify differences in the immune responses of potentially immunosuppressed cancer patients and normal controls, an assessment was made on the effects of the competitive inhibitor alpha-methyl-D-mannoside on the concanavalin A (Con A)-induced blastogenic responses of lymphocytes from each of these populations. Lymphocytes from breast cancer patients with metastatic disease were significantly deficient in their capability to undergo blast transformation regardless of whether the monosaccharide inhibitor was added to the assay cultures. In contrast, lymphocytes from breast cancer patients who did not display metastatic disease were capable of normal blastogenic responses to Con A. The addition of alpha-methyl-D-mannoside to lymphocyte cultures caused a significantly greater inhibition of the blastogenic responses of these patients' cells as compared to cells of normal controls. Thus the monosaccharide seems to serve as a useful reagent for optimizing differences between lymphocyte blastogenic responses of normal donors and those of immunodepressed donors. The results suggest that lymphocytes from breast cancer patients without clinically evident metastases possess some modification of their cell membrane. One possibility discussed was that the number or distribution of receptors for Con A on the membrane of lymphocytes of these patients is deficient. (Author abstract) (27 Refs)

18. ENUMERATION OF LYMPHOCYTES AND THEIR SUBPOPULATIONS IDENTIFIED BY BACTERIAL ADHERENCE IN BLOOD SMEARS OF PATIENTS WITH BREAST TUMORS.

Felix E, Katz S, Teodorescu A, Teodorescu M
(c/o M. Teodorescu) Dept. Microbiology and Immunology, Univ. Illinois Medical Center, Chicago, IL, 60612
J Surg Oncol; 18(4):323-329 1981

Peripheral blood lymphocyte counts were determined in 57 breast clinic patients. These patients were grouped into four clinical/pathological groups: 18 had benign breast disease, 13 had a history of breast cancer but were free of disease at the time of the study, 7 had a history of breast cancer and were free of disease at the time of the study but were on adjuvant chemotherapy, and 19 had active metastatic breast cancer. Two parameters were investigated in a double blind study: (1) the absolute lymphocyte counts and (2) the percentages of lymphocytes that bound different bacteria as markers of lymphocyte subpopulations in conventionally stained blood smears. A significant reduction in mean lymphocyte counts was demonstrated in patients with advanced disease. A significant increase in these counts was found in patients who were free of disease following surgical treatment alone. The T1 T2 cells (our denomination), the subpopulation of cells responsible for specific killing in vitro and for suppression of natural cytotoxic cells, was significantly reduced in patients with advanced disease under treatment. The T/B cell ratio in all groups was the same and within normal range. These observations suggest that the observed decrease in the total lymphocytes is due not only to an overall decrease in all classes of lymphocytes but especially in those responsible for specific cell-mediated reactions. They also show that bacteria can be used as re liable reagents for the identification of lymphocyte subpopulations in blood smears. (Author abstract) (21 Refs)

19. IMMUNE COMPLEX-LIKE MATERIALS IN SERA OF PATIENTS WITH BREAST CANCER: DETECTION BY COMPLEMENT-CONSUMPTION ASSAY.

Sulitzeanu D, Asaf O, Biran S, Brufman G, Gilead Z
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91120 Jerusalem, Israel
Isr J Med Sci; 17(9/10):869-873 1981

Sera of patients with breast cancer were tested for the presence of immune complexes by a complement-consumption assay. To increase the concentration of immune complexes and thus improve the chances of their detection, sera were first ultracentrifuged and the sedimented material was assayed. Sera were considered to be positive if they consumed at least 75% of the hemolytic activity under the conditions of the test. Of the 60 patients tested, 45% were positive as compared with 13.5% positive sera among healthy blood bank donors. The presence of immune complexes could not be correlated with the extent of disease, the age of the patients, treatment or lack of treatment at the time of the test, or the time that had elapsed since diagnosis. In a few control tests, treatment of samples with DNase had no effect on their anticomplementary activity, whereas reduction with 2-mercaptoethanol abrogated the activity. These results strengthened the assumption that the substances binding complement were indeed immune complexes. (Author abstract) (19 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

20. DIHYDROXYANTHRACENEDIONE: A PROMISING NEW DRUG IN THE TREATMENT OF METASTATIC BREAST CANCER.

Yap HY, Blumenschein GR, Schell FC, Buzdar AU, Valdivieso M, Bodey GP
Medical Breast Service, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Ann Intern Med; 95(6):694-697 1981

Thirty-one patients who had metastatic breast cancer extensively pretreated with combination chemotherapy, including doxorubicin, were treated with dihydroxyanthracenedione, 3 to 4 mg/m2 body surface area daily for 5 consecutive days every 4 wk. Of 27 evaluable patients, one achieved a complete response and five had partial responses. Furthermore, responses were seen in patients who were refractory to doxorubicin, indicating a lack of cross-resistance between doxorubicin and dihydroxyanthracenedione. Acute drug toxicity was insignificant except for severe granulocytopenia at the dose level of 4 mg/m2 d. The median duration of remission had not been reached, but was more than 26 wk, with four of the six responding patients still in remission at last follow-up. We believe that dihydroxyanthracenedione has significant activity against refractory metastatic breast cancer and further evaluation is warranted. (Author abstract) (20 Refs)

21. SINGLE AGENT ACTIVITY OF MITOMYCIN C IN BREAST CANCER (MEETING ABSTRACT).

De Lena M, Brandi M, Lorusso V, Colucci G
Medical Branch, Ospedale Oncologico, via Scipione l'Africano, 70100 Bari, Italy
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussells, Belgium European Organization for Research ou Treatment of Cancer; :A6 1981

Despite the encouraging responses obtained in the past yr with daily administration of Mitomycin C (MMC) in metastatic breast cancer, the drug was not widely used because of reported severe myelosuppression. Recently, due to intermittent schedules of administration, the toxicity results were acceptable and new interest for the drug was observed from physicians. The therapeutic activity of MMC in daily administration was high (about 35% objective response) but it is necessary to point out that this percentage was obtained in women mildly pretreated with chemotherapy and, in the major part of the cases, never pretreated with combination chemotherapy. Considering that during the last decade combination chemotherapy was the treatment of choice in metastatic breast cancer, it is clear that, at present, the therapeutic activity of MMC as a single agent in breast cancer can be tested only in women who have become resistant to one or more regimens of polychemotherapy and it can explain the lower percentage of regression actually observed. Nevertheless, it is our opinion that the review regarding the antitumor activity and the toxicity of intermittent schedules of administration of MMC in metastatic breast cancer can provide interesting information about the possible association of the drug with different chemotherapeutic agents. In our experience regarding 24 women treated with MMC (20mg/m2 iv every 6 wk) objective response was observed in 2 cases and stabilization of disease in 5. Leukopenia occurred in 62% of patients and thrombocytopenia in 37%. All the women were previously treated with different combination chemo- and endocrinetherapies. (no Refs)

22. RANDOMIZED PHASE II TRIAL OF CARMINOMYCIN (CMM) VS 4'-EPIADRIAMYCIN (EPIADM) IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

ten Bokkel Huinink W, Pinedo F, Cavalli F, Host H, Dombernowsky P, James K, Renard J, Van Glabbeke M
No affiliation given
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; A59 1981

In this phase II trial, women with advanced breast cancer are randomly allocated to receive CMM or epiADM. If unchanged or progressive disease is noted with these new anthracycline derivatives, treatment is switched to adriamycin (ADM). CMM is given at a dose of 18mg/m2, epiADM at 90mg/m2 and ADM at 75mg/m2. All drugs are given by rapid iv injection repeated every 3 wk. Eligibility criteria include ag e less than or equal to 70 yr, performance status (PS) 50 (Karnofsky), no prior anthracycline therapy, WBC greater than or equal to 4,000/mm3, platelet counts less than or equal to 100,000/mm3, adequate renal and liver function. Thus far, 59 patients (pts) have been entered in the trial and 33 are currently evaluable for response to first-line anthracycline therapy. Partial remission (PR) was obtained in 1 of 17 pts with CMM and in 3 of 16 pts with epiADM. Of 9 pts treated with ADM, only 3 are currently evaluable. One of these achieved PR after having had stable disease with CMM. Myelosuppression is the main toxic effect seen with CMM and epiADM. The median WBC nadir x10(3)/mm3 1.6 with CMM and 1.9 with epiADM.

The corresponding nadirs of the platelet counts are 119 and 142 respectively. Non-hematologic toxic effects of CMM vs epiADM mainly consist of nausea and vomiting alopecia and stomatitis. Two pts had infection and one had bleeding in each treatment arm. Cardiac toxicity has not yet been fully analyzed. Thus, at similar levels of myelosuppression, acute nonhematologic toxic effects encountered with epiADM appear to be very similar to those seen with ADM whereas CMM seems to be better tolerated. (no Refs)

23. HIGH (H) VERSUS LOW (L) DOSE MEDROXYPROGESTERONEACETAT (MPA) IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Cavalli F, Goldhirsch A, Kaplan E, Alberto P
Group for Clinical Cancer Research, 1205 Geneva-CH, Switzerland
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

H dose MPA was recently reported to yield and impressive response rate (RR) in the treatment (Rx) of advanced breast cancer. Therefore 165 postmenopausal patients (pts) with a measurable advanced breast cancer (20% without prior treatment (Rx)) were randomized between 100 mg/daily (H) and 500 g twice weekly (L) MPA im for 4 wk: responding pts were continued on 500 mg MPA im once weekly. During Rx MPA blood levels were determined every 2-4 wk in 9 pts. (5 H, 4 L), in 21 pts (12 H, 9 L) serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E1) and, sex hormone binding hormone (SHBG) were measured monthly. MPA blood levels were consistently and at least twofold higher in pts treated with H, with steady-state levels reached after 4 wk. Preliminary results of the hormonal determinations show a significant decrease of FSH/LH and a marginal increase of PRL during Rx, without clear correlation with H or L dose. At the last cut-off (2/81) 127 pts were already evaluable. Clincal prognostic factors (age, free interval, number and site of metastasis (mets), type of previous Rx and response to it) were well balanced between H and L: Hormone receptors were known only in 1/3 of pts. Partial response (PR) wa s observed in 20/64 (30%) pts with H MPA and 7/62 (11%) in L MPA (RR: H vs L p less than 0.05). The more pronounced difference in RR was found in pts refractory to prior Rx (PR: 12/57 in H, 0/53 in L) or with osseous mets. (PR: 8/20 in H, 1/19 in L). Median duration of PR was 230+ d in H and 150+ d in L. A no change for a median duration of 128 d was observed in 28 pts: 14 in H, 14 in L. These data tend to support the therapeutic superiority of H over L MPA. A final evaluation of all clinical and endocrinologic results is currently underway. (no Refs)

24. ORAL HIGH-DOSE MEDROXYPROGESTERON ACETATE (MPA) IN ADVANCED BREAST CANCER. RETROSPECTIVE EVALUATION OF TWO DIFFERENT SCHEDULES (MEETING ABSTRACT).

Merlano M, CanobbioL, Boccardo F, Guarneri d, Rubagotti A, Rosso R
Istituto Scientifico per lo Studio e la Cura dei Tumori, Genoa, Italy
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The results of a retrospective analysis of the treatment with oral MPA of 50 postmenopausal patients (pts) are reported. Thirty pts (group I) received a median MPA dose of 400mg (range 300-600 mg) bid. Twenty pts (group II) received a single 1g dose per day. In both groups treatment was continued until progression. Both treatment groups are comparable as to age, duration of menopause, disease free interval and previous treatment with chemo and/or conventional hormonal theapy. The 2 groups differ as to dominant site of disease: viscera: I 33%, II 20%; soft tissue: I 41%, II 20%; bone: I 26%, II 60% (P less than 0.05). Ten out of 50 pts showed and objective response to treatment (CR+PR according to UICC criteria): 9/30 pts in group I and 1/20 pts in group II (P less than 0.1). In the overall, 22/30 pts in group I (73%) demonstrated benefit from hormonal therapy showing at least a stationarity of disease compared to 8/20 pts in group II (40%): this difference is significant (P less than 0.05). Median duration of response was 7+mo (range 1-19 mo). Actuarial survival at 30 mo was 37% in group I and 12% in group II respectively (P less than 0.25). In the overall responsive pts showed a significantly longer survival 44% vs 0%: P less than 0.001. In conclusion, the toxicity and the activity of MPA when given po were comparable to the ones reported with the im route. Considering MPA pharmacokinetics when given po, this study seems to suggest that the administration of the drug in at least 2 single refracted doses seems to yield better results. (no Refs)

25. VINDESINE. A PHASE II TRIAL IN ADVANCED BREAST CANCER PATIENTS.

Robins HI, Tormey DC, Skelley MJ, Falkson G, Crowley JJ, Ramirez G, Falkson H
Dept. Human Oncology, Wisconsin Clinical Cancer Center, K4/662 Clinical Science Center, 600 Highland Ave., Madison, WI, 53792
Cancer Clin Trials; 4(4):371-375 1981

A Phase II trial of Vindesine (VDS), a new vinca alkaloid, has been carried out in 40 patients with metastatic breast cancer. Patients entered in the study had been previously treated with an av of two chemotherapy regimens. Treatment was given as a weekly iv bolus of VDS at 3 mg/m2. The response rate in 31 evaluable patients was 19%, ie, one complete response, four partial responses, and one improvement in osseous disease. In 36 patients evaluable for toxicity, neurological and hematological toxicity was most significant. Half the patients treated had received previous vincristine therapy; this factor did not appear significant with regard to toxicity or response to VDS. (Author abstract) (14 Refs)

26. THE LOCAL EFFECT OF INTRA-ARTERIAL CHEMOTHERAPY FOR LOCAL ADVANCED BREAST CANCER: A COMPARISON OF A COMBINATION OF MITOMYCIN C (MMC) AND 5-FLUOROURACIL (5-FU) AND ADRIAMYCIN (ADR) GIVEN SINGLY (MEETING ABSTRACT).

Nishizawa Y, Wada T, Takahashi Y, Koyama H, Terasawa T
Dept. Surgery, Center Adult Diseases, Osaka, Higashinari-ku, Osaka 537, Japan
Program and Preprints of the 3rd Annual Meeting of Japanese Research Society of Intra-arterial Infusion Therapy for Cancer held in Tokyo, 27 June, 1981. Japanese Society of Intra-arterial Infusion Therapy for Cancer, Tokyo 171, Japan, 26 pp., 1981.

As means of multiple therapy for 44 patients with advanced breast cancer seen since 1969, a cannulation was made into the intrathoracic artery and subclavicular artery and the following drugs were injected for 1 to 3 wk. For Group A (29 patients) 375 mg of 5-fluorouracil (5-FU) per day was injected via the above two routes consecutively and 12 mg of MMC intermittently every 3 days (53 mg of mitomycin C (MMC), 6.0 g of 5-FU in all), and for Group B (12 patients) 50 mg of Adriamycin (ADR) was injected singly qod (129 mg in all), via the above two routes. Three patients were given other drugs. Clinically, there was a complete response or partial response in 83% of

Group A patients; histologically the effective rate (IIb or better on Shimosato's classification) was 69%. For Group B these rates were 73% and 82%, respectively, there being no significant difference between the two groups. Although there were more patients in whom an effect was seen when a larger dosage of MMC or ADR was given per day, there was no clear correlation between the total dose and effective rate. The factors that prevented the use of a large dosage were skin disorders and such local side effects as local pain, but these were milder for Group B. The systemic side effects were similar to those observed when the drug was given iv with the dosage reduced to one-half, and they were slightly more severe for Group B. (no Refs) (In JPN)

27. EFFECT OF INTRA-ARTERIAL ADMINISTRATION OF ADRIAMYCIN (ADR) FOR PRIMARY LOCAL ADVANCED BREAST CARCINOMA (MEETING ABSTRACT).

Terasawa T, Abe R, Inoue K, Endo S, Kurokawa Y, Koyama H, Sakai K, Fukami A, Yayoi K
Dept. Surgery, Center for Adult Diseases, Osaka, Higashinari-ku, Osaka 537, Japan

Program and Abstracts of the 34th Meeting of the Japan Mammary Cancer Society held in Tokyo, 4 July, 1981. The Japan Mammary Cancer Society, Maebashi, Gunma Pref. 371, Japan, 53 pp., 1981.

The effect of ia administration of ADR on tumor regression in 35 patients with primary local advanced breast carcinoma was analyzed retrospectively by the Clinical Study Group of Adriamycin for Breast Cancer in Japan. Single administration of ADR was effective in 14/25 patients, and combined ADR and 5-fluorouracil in 2/10 patients. In 25 patients given ADR singly, there was a statistical difference or significant tendency between a dose of 30 mg or less and a dose of over 30 mg, between a tumor more than 5 cm in its greatest diameter and a tumor of any size with direct extension to the chest wall or skin, and between a one-route injection in the subclavian artery and two-route administration into the subclavian and the internal thoracic arteries. A dose of over 30 mg of ADR was more effective than the other doses. It is assumed that the effect of ia ADR injection is closely correlated with the dose given once. The tolerant total dosage was under 150 mg. It is concluded that preoperative ia injection of a 40-to 50-mg dose of ADR two or three times for 7-10 days is most effective for local advanced breast carcinoma. (no Refs) (In JPN)

28. A PHASE II STUDY OF COMBINED 5-FLUOROURACIL AND MITOMYCIN C IN ADVANCED BREAST CANCER.

Mattsson W, Von Eyben F, Hallsten L, Bjelkengren G
Dept. Oncology and Radiotherapy, General Hosp., S-214 01 Malmo, Sweden

Cancer; 49(2):217-220 1982

In a Phase II Study, 50 patients with advanced breast cancer were treated with a combination of 5-fluorouracil (1,000 mg/m2 on days 1 and 2) and mitomycin C (6 mg/m2 on day 2) (FuMi regimen). The courses were repeated every 3rd to 6th wk. Although 35 patients had previously received combination chemotherapy and 40 patients had received endocrine treatment, objective responses were obtained in 29 patients (6 complete, 23 partial). The survival was significantly correlated to the response (p less than 0.001, log rank test) complete versus partial response, partial response versus no change, no change versus progressive disease. The regimen was well tolerated (19 of 50 experienced nausea). Thirteen patients had hematopoietic toxicity at the day of starting a new course and in 6 cases, the FuMi regimen had to be discontinued because of long-lasting thrombocytopenia. Otherwise, no side-effect of clinical importance was observed. The FuMi regimen is now compared with Adriamycin regimens and can be recommended for both first line chemotherapy and salvage chemotherapy. (Author abstract) (20 Refs)

29. PHASE I-II EVALUATION OF COMBINATION CYCLOPHOSPHAMIDE, 5-FLUOROURACIL, HEXAMETHYL-MELAMINE, AND PREDNISONE IN ADVANCED BREAST CANCER.

Chang YC, Falkson G, Tormey DC, Crowley J

(c/o Tormey) Dept. Human Oncology, Univ. Wisconsin Hosp. and Clinics, K4/662 Clinical Science Center, 600 Highland Ave., Madison, WI, 53792

Cancer Clin Trials; 4(4):377-380 1981

A Four-drug combination of intermittent high-dose cyclophosphamide with 5-fluorouracil, hexamethyl-melamine, and prednisone was given to 19 patients with advanced breast cancer. Objective response was documented in 7 of 18 evaluable patients. The median duration of response was 99 days. Response was observed in 6/7 patients without visceral disease and 1/11 patients with visceral disease. Toxicity was acceptable and no life-threatening toxicity was observed. Three patients had received the four-drug combination for more than 1 yr without serious side effects. This regimen may serve as an alternative treatment for patients without visceral metastasis who have failed to respond to other combination chemotherapy regimens. (Author abstract) (12 Refs)

30. MULTIMODAL THERAPY WITH CMF IN RESECTABLE BREAST CANCER WITH POSITIVE AXILLARY NODES: THE MILAN INSTITUTE EXPERIENCE.

Bonadonna G, Valagussa P, Rossi A, Tancini G, Brambilla C, Marchini S, Veronesi U

Div. Medical Oncology, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milan, Italy

Recent Results Cancer Res; 80:149-156 1982

The effect of multimodal therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF therapy) was tested in patients following radical mastectomy (RM) for breast cancer. Six-yr survival rates (6SR) were 73.9% for patients receiving 12 cycles of CMF (12CMF) and 64.5% for those receiving only RM. Relapse-free survival (RFS) was significantly different for the two treatment groups in patients with one to three involved lymph nodes (N1: 65.1% after RM and CMF; 45.6% after RM) and among premenopausal patients (59.8% after RM and CMF; 42.7% after RM). In a second study no differences were found between 12CMF patients and those receiving only six cycles of CMF. A study of 115 patients treated with six cycles of CMF followed by four cycles of adriamycin plus vincristine showed no advantage of sequential combination therapy over previously reported CMF therapy. Combining low-dose 12CMF with tamoxifen (20 mg/day for 12 mo) produced an RFS of 90.6% among patients greater than 65 yr old (95.6% among N1 patients greater than 65 yr old). Final results from the group are not available. General response to CMF was dose-dependent. Constant administration of full doses is therefore recommended; if myelosuppression occurs, treatment should be delayed rather than reduced. Estrogen-receptor status is apparently not useful in predicting RSF fol lowing CMF. (15 Refs)

31. TAMOXIFEN (T) VERSUS AMINOGLUTETHIMIDE (AG) VERSUS COMBINED TAMOXIFEN AND AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Smith IE, Harris AL
Breast Unit, Royal Marsden Hospital, Fulham Road, London, England
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

One hundred and seventeen patients with advanced breast cancer were entered into a control randomized cross-over trial comparing T 10 mg x 2 daily with AG 250 mg x 4 and hydrocortisone 20 mg x daily. Patients failing to respond to one treatment or relapsing were switched to the other. Eighteen (30%) of the 60 patients initially treated with T achieved an objective response, and 11 (18%) showed stable disease. Seventeen (30%) of the 57 patients initially treated with AG achieved an objective response and 13 (23%) achieved stable disease. Five (17%) of 29 patients with bone metastases achieved an objective response to T compared with 11 (35%) of 31 treated with AG. No difference has so far been seen in predicted median response duration (15 mo for both drugs) or for survival. Five (15%) of 34 patients failing to respond to T subsequently responded to AG; 4 of 6 patients relapsing after response to T achieved a second response to AG. In contrast only 2 (6%) of 31 patients failing to respond to AG subsequently respnded to T and O out of 4 patients relapsing after AG achieved a second response to T. Toxicity, including drowsiness and/or rash, was commoner in AG-treated patients, and 5 (9%) had to discontinue treatment because of this, compared with none on T. In a sequential study 62 patients have been treated with combined T and AG in the same dose as above. Fourteen (29%) of 49 patients so far assessable have achieved an objective response and 6 (12%) stable disease. In conclusion, AG is as effective as T for advanced breast cancer and may be superior for bone metastases, but is more toxic. Combining the 2 agents does not appear to achieve a higher response rate. (no Refs)

32. MEDICAL ADRENALECTOMY WITH AMINOGLUTETHIMIDE AFTER PRIOR TREATMENT WITH TAMOXIFEN IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Robin ML, Pitt M, Pitt P
Endocrine Unit, Cancer Institute, Melbourne, Australia
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The role of medical adrenalectomy in advance breast cancer in patients who have previously been treated with the anti estrogen tamoxifen is not well defined. Seventy-one patients who had actively progressing metastatic breast cancer and who had all received prior treatment with tamoxifen were treated with aminoglutethimide (A/G) to induce a medical adrenalectomy. Classification of response was carried out according to International Union Against Cancer criteria. Medical adrenalectomy was induced with a dose of A/G sufficient to cause at least a 50% fall in dehydroepiandrosterone-sulfate. Twenty seven patients had responded to tamoxifen and then relapsed; of these, 17 (63%) experienced further remission when treated with A/G. Forty four patients had not responded to tamoxifen, and of these 16 (36%) subsequently responded when treated with A/G. These response rates are significantly different (p less than 0.05). The median duration of remission to tamoxifen was 14 mo, but there was no relationship between the duration and the likelihood of subsequent response to A/G. The median duration of response to A/G was 12 mo (range 4-30+ mo). The high response rate to A/G in patients who have previously responded to tamoxifen, together with the good tolerance of the drug make medical adrenalectomy the treatment of choice in tamoxifen responsive patients. Failure to respond to tamoxifen should not preclude treatment with A/G as up to 36% of patients may experience remission. The data suggests that tamoxifen and A/G may act through different mechanisms. (no Refs)

33. TAMOXIFEN PLUS CIVEFU VS CIVEFU IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Galmarini F, Santos F, Bruno R, Casas R, Chiesa O, Bertacchini J, D'Auria A, Dominguez E
Munucipal Hospital of Oncology, Buenos Aires, Argentina
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In order to determine whether the addition of Tamoxifen to the chemotherapy in patients with advanced breast cancer improve the results, since October 1979 we have treated 133 patients, chosen at random and divided into two groups: (A) 64 who received Fluorouracil (600 mg/m2/days 1 to 5); Cytoxan (400 mg/m2/day 1) and Velbe (6 mg/m2/day 1) (CIVEFU): (B) 69 patients with the same scheme plus 30 mg, day of Tamoxifen (Protocol 4002-OSITC). Grading was keeping with hormonal status, interval free from lesions and metastasis sites. Thirty five patients (54.6%) had response (R), while 14 (21.8%) registered complete response (CR) in Group A. In Group B, 46 (66.6%) registered R while 22 (31.8%) had CR. These results considered 'in toto' did not differ in statistical significance. Neither were significant differences betwen pre- and perimenopausic cases, as compared with the post-menopausic ones in both groups and the individual ones. There were significant differences in the CR of soft tissues (20.8% in A and 45.8% in B) and in R of bone metastases (26.6% in A and 57.8% in B). No significant differences were established in the case of metastases to lungs, liver, brain and pleural effusion. It was concluded that the incorporation of Tamoxifen to chemotherapy treatments improved results in soft tissue and bone metastases. (no Refs)

34. CONSERVATIVE TREATMENT FOR BREAST CANCER OF LIMITED EXTENT. RESULTS OF A RANDOMIZED TRIAL.

Veronesi U, Del Vecchio M, Greco M, Luini A, Muscolino G, Rasponi A, Saccozzi R, Zucali R
Istituto Nazionale Tumori, via Venezian 1, 20133 Milan, Italy
Isr J Med Sci; 17(9/10):928-931 1981

From 1973 to 1980, a controlled clinical trial was carried out at the National Cancer Institute of Milan to compare the Halsted mastectomy with breast quadrantectomy and axillary dissection followed by radiotherapy in patients with breast cancer of less than 2 cm in size. Cases of breast cancer classified as T1N0 were randomized into the two treatment procedures: 349 cases were treated with the Halsted mastectomy and 352 with the quadrantectomy technique. The two series were comparable with regard to age distribution, size, site of primary tumor, menopausal status and frequency of axillary metastases. Three local recurrences occurred in the Halsted group and one in the quadrantectomy group. Actuarial curves showed no difference in the two series with regard to disease-free and overall survival. In view of these results, mastectomy appears to be an unnecessary mutilation for patients with breast carcinomas less than 2 cm in size and no palpable axillary nodes. (Author abstract) (18 Refs)

35. A RANDOMIZED TRIAL OF POSTOPERATIVE FIVE-VERSUS THREE-DRUG CHEMOTHERAPY AFTER MASTECTOMY: A CANCER AND LEUKEMIA GROUP B (CALGB) STUDY.

Weiss RB, Tormey DC, Holland F, Weinberg VE, Lesnick G, Perloff M, Falkson G, Glidewell OJ
Clinical Investigations Branch, NCI, Bethesda, MD, 20205
Recent Results Cancer Res; 80:170-176 1982

The Cancer and Leukemia Group B (CALB) has conducted a randomized study of adjuvant chemotherapy in patients with breast cancer who have involved axillary nodes at the time of mastectomy. Five-drug treatment (CMFVP) was compared with three-drug treatment (CMF). For patients with more than three involved nodes, the CMFVP regimen produced a significantly prolonged disease-free survival in comparison to the CMF regimen. (Author abstract) (6 Refs)

36. RADIATION THERAPY WITH OR WITHOUT PRIMARY LIMITED SURGERY FOR OPERABLE BREAST CANCER: A 20-YEAR EXPERIENCE AT THE MARSEILLES CANCER INSTITUTE.

Amalric R, Santamaria F, Robert F, Seigle J, Altschuler C, Kurtz JM, Spitalier JM, Brandone H, Ayme Y, Pollet JF, Burmeister R, Abed R

(c/o Spitalier) Dept. Radiotherapy, Mareilles Cancer Inst., BP 156 F13273, Cedex 02 Marseilles, France
Cancer; 49(1):30-34 1982

Since 1960 more than 3,000 consecutive patients with operable infiltrating breast carcinoma were treated by radiation therapy with or without primary limited surgery, which usually consisted of local excision. For tumors smaller than or equal to 5 cm the 10-yr crude survival rate is 77% for pa tients without palpable axillary nodes (T1-2N0) and 63% for patients having axillary adenopathy (T1-2N1). For operable tumors exceeding 5 cm in diameter (T3N0-1) the 10-yr crude survival is 34%. Thirty-five percent of the patients alive free of disease at 10 yr required a secondary operation for presumed local or regional tumor persistence or recurrence, although no residual disease was found in 24% of the operative specimens. Local-regional recurrence had no adverse effect on 10-yr survival. This conservative approach offers most women with operable breast cancer and excellent chance at breast preservation with the same chance for 10-yr survival as with radical mastectomy. (Author abstract) (36 Refs)

37. ADJUVANT TAMOXIFEN TREATMENT OF POSTMENOPAUSAL, HIGH RISK BREAST CANCER PATIENTS (MEETING ABSTRACT).

Mouridsen HT, Thorpe SM, Roe C, Andersen J, Brincker H, Andersen KW
Danish Breast Cancer Cooperative Group (DBCG) Secretariat, Finsen-institute, 2100 Copenhagen, Denmark
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Ninety-five % of all primary breast cancer patients (pts) in Denmark are centrally registered and given the same surgical treatment (total mastectomy and partial axillary dissection). Seventy % of these pts fulfill the criteria for entrance into prospective adjuvant trials. The trial described here includes postmenopausal (greater than 5 yr since last menstruation) node positive pts. These were randomized to receive either radiotherapy alone (RT) or RT plus Tamoxifen 10 mg tid, for one yr (RT+ TAM). From Oct 1977 to May 1981 982 pts have entered this trial. The recurrence rates are presently 34% for the RT group and 24% for the RT+TAM group. With respect to age, a significantly lower recurrence rate is observed from women under 70 who are treated with RT+TAM than with RT alone, while no difference is observed in women over 70. With respect to tumor anaplasia, the rate of recurrence is lower in each of the 3 World Health Organization tumor grade classifications in women treated with RT+TAM compared to those treated with RT alone. An increasing percentage of pts now approx 60% have receptor determination performed on their biopsies. Presently estrogen receptor (ER) data is available for 132 pts that have been observed from 0-1 1/2 yr. (no Refs)

38. ORAL LMF ADNUVANT CHEMOTHERAPY: ADDITIONAL EVIDENCE FOR ITS EFFICACY IN NODAL-NEGATIVE BREAST CANCER (MEETING ABSTRACT).

Schmid L, Jungi WF, Senn HJ

Medizinische Klinik C, Kantonsspital, CH-9007 St. Gallen, Switzerland

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Oral LMF (Chlorambucil, Amethopterine and 5-Fluorouracil) have been shown to be an effective and safe adjuvant chemotherapy regimen for nodal-negative breast cancer patients (OSAKO-trial, Senn, ASCO 1981, C-366). To confirm these results we have treated in a 2nd prospective non-randomized study 58 women with radically operated breast cancer of stage T 1-3a NOMO. Oral intermittent chemotherapy with LMF was given as in the OSAKO-Trial for 6 mo (but without BCG). Of the 58 evaluable patients (mean age 52.4 yr) 34 were pre- or peri- and 24 post-menopausal. Twenty-eight were tumor stage T1, 19 stage T2, 3 T3 (9 not classifiable).Mean observation time at the least analysis (December 31, 1980) is 17 mo. We have observed 8 relapses so far, 2 at loco-regional and 6 at distant sites (all in the bone) Two of the relapsing patients were pre-, 6 postmenopausal. Two of them were T1, 4 T2 and 2 T3. Rates of tumor-free survival are after 1 yr 0.95 (1.00-0.81) and after 2 yr 0.80 (0.96-0.63). Toxicity was minimal, leukothrombopenia led to dose modification in some patients. The beneficial effect of oral LMF in the prevention of tumor firmed, especially in premenopausal patients. (1 Ref)

39. A NEW ADJUVANT TREATMENT WITH POLYADENYLIC-POLYURIDYLIC ACID IN OPERABLE BREAST CANCER.

Lacour F, Lacour J, Spira A, Michelson M, Delage G, Petit JY, Viguier J

Laboratoire d-Immunologie, Institut Gustave-Roussy, 16 bis Avenue Paul Vaillant-Couturier, F-94800 Villejuif, France

Recent Results Cancer Res; 80:200-206 1982

Adjuvant treatment with polyadenylic-polyuridylic acid poly A-poly U was tested in 300 patients with operable breast cancer who had all received the same locoregional treatment. They were randomized into two groups; 155 patients receiving 30 mg poly A-poly U iv once a wk for 6 wk and 145 controls. Overall survival was significantly improved in the poly A-Poly U group (p less than 0.05). The most striking difference (p less than 0.03) was observed in the group of positive node patients, who had a 5-yr relapse-free actuarial survival rate of 71% vs 47% in the controls. (Author abstract) (14 Refs)

40. ADJUVANT TREATMENT OF NODE-POSITIVE BREAST CANCER WITH ADRIAMYCIN-CYCLOPHOSPHAMIDE WITH OR WITHOUT RADIATION THERAPY: INTERIM RESULTS OF AN ONGOING CLINICAL TRIAL.

Jones SE, Salmon SE, Allen H, Giordano GF, Davis S, Chase E, Moon TE, Heusinkveld RS

Dept. Internal Medicine, Section Hematology/Oncology, Arizona Health Sciences Center, Tucson, AZ, 85724

Recent Results Cancer Res; 80:162-169 1982

During 1974-1980, 138 women with node-positive Stage II breast cancer were treated with either eight courses of adriamycin-cyclophosphamide (AC) chemotherapy (82 patients) or AC chemotherapy plus comprehensive regional radiotherapy (56 patients). The overall relapse-free survival of the treated patients was significantly superior (p less than 0.001) to a comparable group of women who underwent surger y alone. This effect of adjuvant therapy was clearly manifest in all groups of patients irrespective of nodal involvement of menopausal status. To date, relapse-free survival for patients receiving AC compared to AC plus radiotherapy is not different ($p = 0.7$). In summary, we have demonstrated that a brief 6-mo course of adjuvant chemotherapy with AC can significantly reduce the recurrence rate in women with Stage II breast cancer. (Author abstract) (21 Refs)

41. DEVELOPMENT OF A NATURAL HISTORY DATA BASE (NHDB) AND ITS COMPARISON TO SELECTED ADJUVANT FOR BREAST CANCER (MEETING ABSTRACT).

Moon T, Jones S, Davis S, Bonadonna G, Valagussa P, Powles T, Rivkin S

University of Arizona Cancer Center, Tucson, AZ

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We have developed a composite data base for breast cancer which has been used to evaluate the natural history and the effect of various adjuvant therapies. Complete information was collected on prognostic factors for 1,305 tumor, node, metastases Stage I+II patients who received surgery +/- postoperative x-ray therapy (XRT). Similar information was collected from several ongoing adjuvant trials involving 1,259 Stage II patients. Retrospective analyses adjusted for prognostic factors were carried out. The number of nodes involved and tumor size were related to relapse-free survival (RFS) and overall survival (S) for patients in the NHDB and yielded prognostically different patient groupings. Each adjuvant treatment group was compared to the NHDB in terms of RFS and S. The most important prognostic factor was the number of nodes involved Menopausal status and tumor size did not effect prognosis in adjuvant treated patients. The single agent L-phenylalanine mustard (L-PAM) (141 patients) yielded only minimal adjuvant effect while cyclophosphamide, methotrexate, 5-fluorouracil (CMF) (645 patients), cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) (314 patients) and adriamycin, cyclophosphamide (AC)+/-XRT (159 patients) yielded significant increases in RFS and S. Ajuvant effect was seen in all postmenopausal patients treated with greater than or equal to 2 drugs. Assessment of relative treatment effect, and number of agents will also be discussed. (no Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

42. AGE AT MENARCHE, PROBABILITY OF OVULATION AND BREAST CANCER RISK.

MacMahon B, Trichopoulos D, Brown J, Andersen AP, Aoki K, Cole P, DeWaard F, Kauraniemi T, Morgan RW, Purde M, Ravnihar B, Stormby N, Westlund K, Woo NC

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115

Int J Cancer; 29(1):13-16 1982

An analysis is undertaken of the frequency of ovulation in 17 groups of women ag ed 15 to 19 who had been the subjects of other studies. A urine specimen of at least 8 hr accumulation had been provided on the 20th or 21st day of a menstrual cycle by 681 women. Analysis is restricted to 431 specimens which had been collected between 11 and 3 days prior to the onset of the subsequent menstrual period. A pregnanediol concentration of less than 1 mg/l in such a specimen was taken as evidence that the cycle was anovular. The probability of a cycle being anovular was inversely and significantly related to the number of yr since menarche, and, with yrs since menarche held constant, was positively but not significantly associated with age at menarche. This observation indicates that women with early menarche do not have a longer duration of exposure to anovular cycles than do those whose menarche is delayed, and that variation in the duration of exposure to post-menarcheal anovular cycles does not explain the association of breast cancer risk with early age at menarche. The 17 groups of women were classified into four categories according to ethnic origin and breast cancer incidence in the populations from which they derived. Anovular cycles were not more common in the high-risk groups; indeed, the two centers in the lowest risk category had the highest proportion of anovular cycles. (Author abstract) (15 Refs)

43. EPITHELIAL DYSPLASIA IN NIPPLE ASPIRATES OF BREAST FLUID: ASSOCIATION WITH FAMILY HISTORY AND OTHER BREAST CANCER RISK FACTORS.

Petrakis NL, Ernster VL, King EB, Sacks ST

Dept. Epidemiology and International Health, Univ. California, 1699 HSW, San Francisco, CA, 94143

JNCI; 68(1):9-13 1982

Because of the strong association of epithelial dysplasia and breast cancer, the extent to which dysplasia of breast fluid epithelial cells obtained by nipple aspiration is associated with breast cancer risk factors was investigated. A significantly higher proportion of women who had a first-degree family history of breast cancer had dysplastic cells in breast fluid than women who had no such history. When family history status was correlated with various breast cancer risk factors, higher proportions of women with dysplasia were found among those who had a first degree family history of breast cancer and for whom certain other risk factors were present, which suggested additive and synergistic effects of these factors on breast epithelium. Breast epithelia of women with a first-degree family history of breast cancer may be more prone to abnormal differentiation in response to environmentally conditioned risk factors. (Author abstract) (28 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

44. DIAGNOSIS OF PRIMARY BREAST CARCINOMA THROUGH IMMUNOHISTOCHEMICAL DETECTION OF ANTIGEN RELATED TO MOUSE MAMMARY TUMOR VIRUS IN METASTATIC LESIONS: A REPORT OF TWO CASES.

Mesa-Tejada R, Oster MW, Fenoglio CM, Magidson J, Spiegelman S
Inst. Cancer Res., 701 West 168th St., New York, NY, 10032
Cancer; 49(2):261-268 1982

Recent investigations have established that approximately half of human breast carcinomas contain an immunohistochemically detectable antigen which is cross-reactive with the 52,000-dalton major glycoprotein (gp52) of the mouse mammary tumor virus (MMTV). This antigen can be localized in paraffin-embedded sections of routinely fixed tissues using heterologous antibodies to gp52 or MMTV. This report describes two patients with metastatic carcinoma in axillary lymph nodes without any clinical evidence of a primary lesion in the breast or elsewhere. The localization of the gp52-related antigen in paraffin-embedded sections of both metastatic lesions suggested the presence of primary mammary carcinoma. In both instances, this suggestion was ultimately confirmed by the finding of primary lesions in which the gp52-related antigen was also found. (Author abstract) (30 Refs)

45. USE OF AN EFFICIENT METHOD FOR CULTURING HUMAN MAMMARY EPITHELIAL CELLS TO STUDY ADRIAMYCIN SENSITIVITY.

Smith HS, Hackett AJ, Lan S, Stampfer MR
Peralta Cancer Res. Inst., 3023 Summit St., Oakland, CA, 94609
Cancer Chemother Pharmacol; 6(3):237-244 1981

Techniques for isolating, cryopreserving, and culturing human mammary epithelial cells of both normal and malignant origin are described. The cells can be grown either in mass culture or as a clonal assay suitable for quantitating drug sensitivity. Human mammary epithelial cells were cultured under clonal and mass culture conditions. Planting efficiencies of 6-41% were routinely obtained with the clonal assay. The specimens which grew in mass culture grew also in the clonal assay. The cells were cuboidal in shape and lacked anti-hemophilic factor VIII antigen. The responses of five different primary carcinoma cultures from patients without prior drug therapy to adriamycin were summarized. The effects of adriamycin on two cultures, 72T and 173T were examined by evaluating 9 or 10 randomly selected colonies for the number of cell/colony 6 days post seeding. The mean number of cells/colony was lower in drug-treated dishes. Some of the colonies surviving drug treatment were quite large. Heterogeneity in response to adriamycin among the breast carcinoma cultures was detected. Heterogeneity among subpopulations within a single carcinoma was also detected. The differences in adriamycin sensitivity were unrelated to growth rates in culture. (18 Refs)

46. EFFECTS OF THIOTEPA ON PRIMARY CULTURES OF DMBA-INDUCED MAMMARY TUMOURS OF RATS: KINETICS AND ULTRASTRUCTURE.

Fink SM, Tseng MT
Dept. Anatomy, Univ. Louisville, Louisville, KY, 40292
Br J Cancer; 44(5):762-765 1981

Effects of thiotepa (TP) on growth kinetics, thymidine labeling index (LI), and fine structure of cells cultured from mammary tumors induced by 7,12-dimethylbenz(alpha)anthracene (DMBA) in female Sprague-Dawley rats were determined. Cell subpopulations of these tumors were separated by isopycnic centrifugation. Primary cell cultures were obtained from band 3. Of the three parameters measured, the most obvious TP (10(-2) 10(-6) M)-induced changes were in the rate of DNA synthesis as determined by LI. At 10(-2) M TP, none of the remaining attached cells incorporated (3H)thymidine during pulse labeling. While the percentage of cells in S phase closely approximated the percentage of attached cells after treatment with 10(-6) M TP, the LI curve declined more sharply than the dose-response curves. Ultrastructural analysis revealed no viable cells remaining after 10(-2) M TP. At the lowest TP concentration (10(-6) M), the cells could not be distinguished from controls on the basis of fine structure. Cell-kinetic data indicated that growth inhibition of the selected DMBA-induced tumor cell subpopulation in culture by TP is dose-dependent. A good correlation was found between cell kinetics and labeling index. Indirectly, the study supports the concept of cell heterogeneity in solid tumors. (9 Refs)

47. INFLUENCE OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON ESTROGEN AND PROGESTIN BINDING PROTEINS IN UTERI AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS OF THE RAT.

Heidemann PH, Wittliff JL, Calhoon RE, Boylan ES
(c/o Wittliff) Dept. Biochemistry, Health Sciences Center, Louisville, KY, 40292
J Toxicol Environ Health; 8(4):667-686 1981

Various characteristics of steroid binding proteins from mammary tumors and from uteri of rats exposed prenatally to diethylstilbestrol (DES) were examined. Pregnant rats were treated with no hormone (group A) or with a total dose of 1.2 ug DES during the second (group B) or third (group C) trimester of gestation. Female offspring received 7,12-dimethylbenz(a)anthracene (DMBA) at day 50 +-1. Animals with large mammary tumors were subjected to bilateral ovariectomy. The experiment was terminated 7 mo after carcinogen treatment. High-affinity binding sites for (3H)estradiol-17beta and (3H)R5020 were found in all mammary tumors assayed. Estrogen receptor forms 8S and 4S were identified on sucrose gradients of low ionic strength regardless of prenatal treatment. Progestin receptors (PR) sedimenting at 4S were also identified in the tumors. PR form 7-8S was found only in tumors from intact animals. PR levels diminished after ovariectomy in mammary tumors and in uteri. Uterine progestin binding capacities and uterine wet wt did not decrease proportionally after ovariectomy in group C. PR capacities in mammary tumors from group C were higher than in other groups. Cytosol from mammary tumors in group C intact rats also had elevated PR levels. Uterine estrogen binding capacities did not vary significantly. Prenatal exposure to DES during the third trimester appeared related to persistent biochemical alterations in rat mammary tumors and uteri. Earlier exposure did not have the same effect. (61 Refs)

48. CALCITONIN INDUCTION OF A PERSISTENT ACTIVATED STATE OF ADENYLATE CYCLASE IN HUMAN BREAST CANCER CELLS (T 47D).

Lamp SJ, Findlay DM, Moseley JM, Martin TJ
(c/o Martin) Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria 3081, Australia

J Biol Chem; 256(23):12269-12274 1981

In a calcitonin-responsive human breast cancer cell line (T 47D), specific receptors exist for calcitonin in intact cells, which show saturable binding which is only slowly and incompletely reversible. Full stimulation of cyclic AMP production in the cells was achieved with less than 50% receptor occupancy. Pretreatment of cells in culture with calcitonin, followed by washing, led to loss of adenylate cyclase response to calcitonin in homogenates. This took place rapidly, reaching a maximum after 15 min of preincubation with 3 nM salmon calcitonin, and was associated with a substantial increase in basal adenylate cyclase activity, which was dose-dependent and agonist-specific, in that it did not occur upon treatment of the cells with prostaglandin E2. Receptor loss, as measured by decrement in specific binding of [^{125}I]calcitonin to intact cells, took place more slowly, requiring at least 1 hr for completion. Recovery of adenylate cyclase responsiveness and return of basal activity to normal was a relatively slow process, always requiring more than 24 hr for completion. Neither the desensitization nor the persistent basal activity could be transferred in the cytosol compartment of calcitonin-preincubated cells. When calcitonin-preincubated cells were washed, and at intervals thereafter, the production of cyclic AMP was measured in the presence of a phosphodiesterase inhibitor, a 120-fold rise in basal cyclic AMP production was observed, and the response to added calcitonin was lost. Return of basal activity and of calcitonin responsiveness followed a time course similar to that seen in recovery of adenylate cyclase response. The results indicate the ability of calcitonin to induce rapidly a persistent state of adenylate cyclase activation which remains stable for several hours. This may be due to persistent tight binding of calcitonin but may also be related to changes induced by calcitonin in availability or function of nucleotide regulatory units. (Author abstract) (34 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abe R 27
Abed R 36
Alberto P 23
Allen H 40
Altschuler C 36
Amalric R 36
Andersen AP 42
Andersen J 37
Andersen KW 37
Aoki K 42
Asaf O 19
Ayme Y 36
Ben-David M 8
Bertacchini J 33
Biran S 19
Biran S 8
Bjelkengren G 28
Blumenschein GR 20
Boccardo F 24
Bodey GP 20
Bonadonna G 30
Bonadonna G 41
Bowen JH 6
Boylan ES 47
Brambilla C 30
Brandi M 21
Brandone H 36
Brincker H 37
Brown J 42
Brufman G 19
Bruno R 33
Burmeister R 36
Buzdar AU 20
Calhoon RE 47
CanobbioL 24
Casas R 33
Cavalli F 22
Cavalli F 23
Chaimoff C 11
Chang YC 29
Chase E 40
Cheresh DA 17
Chiesa O 33
Clark JH 10
Cole P 42
Colucci G 21
Coulson PB 12
Crowley J 29
Crowley JJ 25
D'Auria A 33
Davis S 40
Davis S 41
De Lena M 21
DeWaard F 42
Dean PB 5
Del Vecchio M 34
Delage G 39
Distasio JA 17
Dombernowsky P 22
Dominguez E 33
Dror Y 8
Endo S 27
Ernster VL 43
Falkson G 25
Falkson G 29
Falkson G 35
Falkson H 25
Felix E 18
Feller N 11
Fenoglio CM 44
Findlay DM 48
Fink SM 46
Friedman AK 4
Fukami A 27
Galmarini F 33
Gefter WB 4
Gilead Z 19
Gioffre Florio 7
Giordano GF 40
Giorgianni G 7
Glidewell OJ 35
Goldhirsch A 23
Goodman RL 4
Greco M 34
Guarneri d 24
Gustafsson JA 16
Gustafsson S 16
Hackett AJ 45
Halbrecht I 11
Hallsten L 28
Harris AL 31
Hartveit F 2
Heidemann PH 47
Heusinkveld RS 40
Holland F 35
Hortobagyi GN 3
Host H 22
Inoue K 27
James K 22
Johansen P 9
Jones S 41
Jones SE 40
Jungi WF 38
Kaplan E 23
Katz S 18
Kauraniemi T 42
King EB 43
Koyama H 26
Koyama H 27
Kupfer B 14
Kurokawa Y 27
Kurtz JM 36
Lacour F 39
Lacour J 39
Lamp SJ 48
Lan S 45
Lesnick G 35
Levine SE 15
Libshitz HI 3
Ljung BM 16
Lopez DM 17
Lorusso V 21
Luini A 34
MacMahon B 42
Magidson J 44
Malachi T 11
Marchini S 30
Martin TJ 48
Mattsson W 28
McCarty KJ 6
McCarty KS 15
McCarty KS 15
Merlano M 24
Mesa-Tejada R 44
Micali B 7
Michalopoulos G 15
Michelson M 39
Moon T 41
Moon TE 40
Morgan RW 42
Moroz C 14
Moseley JM 48
Mossler JA 6
Mouridsen HT 37
Muscolino G 34
Mygind H 9
Nenci I 13
Nishizawa Y 26
Nordenskjold B 16
Oster MW 44
Panko WB 10
Paulsen SM 9
Pavlov KA 1
Perloff M 35
Petit JY 39
Petrakis NL 43
Pinedo F 22
Pitt M 32
Pitt P 32
Pollet JF 36
Powles T 41
Purde M 42
Ramirez G 25
Rasmussen KS 9
Rasponi A 34
Ravnihar B 42
Renard J 22
Rivkin S 41
Robert F 36
Robin ML 32
Robins HI 25
Roe C 37
Rossi A 30
Rosso R 24
Rubagotti A 24
Saccozzi R 34
Sacks ST 43
Saitta FP 7
Sakai K 27
Salmon SE 40
Santamaria F 36
Santos F 33
Schell FC 20
Schilder RJ 17
Schmid L 38
Seigle J 36
Semiglazov VF 1
Senn HJ 38

Silfversward C 16
Silverman MA 17
Skelley MJ 25
Skoog L 16
Smith HS 45
Smith IE 31
Spiegelman S 44
Spira A 39
Spitalier JM 36
Stampfer MR 45
Stormby N 42
Sulitzeanu D 19
Tabar L 5
Takahashi Y 26
Tancini G 30
Ten Bokkel Huin 22
Teodorescu A 18
Teodorescu M 18
Terasawa T 26
Terasawa T 27
Thornthwaite JT 12
Thorpe SM 37
Tormey DC 25
Tormey DC 29
Tormey DC 35
Trichopoulos D 42
Tseng MT 46
Valagussa P 30
Valagussa P 41
Valdivieso M 20
Van Glabbeke M 22
Venuti A 7
Veronesi U 30
Veronesi U 34
Viguier J 39
Vogel CL 17
Von Eyben F 28
Wada T 26
Wallgren A 16
Watson CS 10
Weinberg VE 35
Weiss RB 35
Westerberg H 16
Westlund K 42
Wittliff JL 47
Woo NC 42
Wrange O 16
Yap HY 20
Yayoi K 27
Zucali R 34

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INTERNATIONAL CANCER RESEARCH DATA BANK

BREAST CANCER

Diagnosis, Treatment, Pre-Clinical Biology

SERIES CT09 No. 82/06

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)........ 1-2
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS........ 3-7
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS........ 8-14
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS........ 15-16
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)........ 17-27
- REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT........ 28-31
- SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)........ 32
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY........ 33-34
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)........ 35-36

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HE 20. 3173/2:

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. MASS SCREENING OF HEALTHY SUBJECTS.

Capdeville R, Remy J
Service de Radiologie, Hopital International de l'Universite de Paris, 42, boulevard-Jourdan, F 75014 Paris, France
J Radiol; 62(11):573-577 1981

Advantages and disadvantages of radiological screening for individuals at risk such as: lung radiography for tuberculosis, radiological evaluation of the pelvis for infants with suspected hip malformations, and use of mammography for the detection of breast cancer are discussed. For women less than 35 yr old, the risks of yearly mammography equal the risks of breast cancer. For women between 35 and 44 yr old, the benefits of mammography are significant. It has been calculated that an additional 68/100,000 lives could be saved by routine mammographic examination as compared with a population in which screening was not performed. Radiation dosages administered in the three technics are considered. Future dose reductions are expected in these diagnostic procedures. It was concluded that the three examinations are justified, but that it is necessary to accurately determine the at risk populations and to minimize exposure doses. (20 Refs) (In FRE)

2. SCREENING FOR BREAST CANCER IN A HIGH-RISK SERIES.

Woodard ED, Hempelmann LH, Janus J, Logan W, Dean P
Univ. Rochester Sch. Medicine and Dentistry, P.O. Box 307, 601 Elmwood Ave., Rochester, NY, 14642
J Surg Oncol; 19(1):31-35 1982

A unique cohort of women at increased risk of breast cancer because of prior x-ray treatment of acute mastitis and their selected high-risk siblings were offered periodic breast cancer screening including physical examination of the breasts, mammography, and thermography. Twelve breast cancers were detected when fewer than 4 would have been expected based on age-specific breast cancer detection rates from the National Cancer Institute/American Cancer Society Breast Cancer Demonstration Detection Projects. Mammography was positive in all cases but physical examination was positive in only three cases. Thermography was an unreliable indicator of disease. Given the concern over radiation-induced risk, use of low-dose technique and of criteria for participation that select women at high risk of breast cancer will maximize the benefit/risk ratio for mammography screening. (Author abstract) (12 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

3. BREAST PARENCHYMAL PATTERNS: ANALYSIS OF 332 INCIDENT BREAST CARCINOMAS.

Wolfe JN, Albert S, Belle S, Salane M
Dept. Radiology, Hutzel Hosp., 4707 St. Antoine, Detroit, MI, 48201
AJR; 138(1):113-118 1982

A detailed analysis of 332 incident breast carcinomas is presented. The study results indicate that there is validity to the breast parenchymal patterns as an indication of risk for developing breast cancer and that risk is independent of length of follow-up and age of patient. All cases were drawn from a referral-type practice at Hutzel Hospital, Detroit, Michigan. The cases were compared to controls for computation of relative risk up to and beyond a follow-up period of 48 mo. They were also compared to a consecutive series of prevalent breast carcinomas seen at Hutzel Hospital during the 6 yr 1975-1980. The extent of disease in the cases described in this report is somewhat more favorable than in a consecutive series of prevalent cancers operated on at Hutzel Hospital. Most breast cancers occur in the P2 breast, a smaller number in the DY, and only 12% in the combined N1P1 type. The conclusions of other investigators regarding parenchymal patterns as risk indicators are reviewed. Particular attention was paid to comparing the length of follow-up and age of patient. There was no diminution of proportions of cases in the P2/N1-P1 or DY/N1-P1 after a 48 mo follow-up. There was a significant diminution in the proportion of cases falling into DY/N1-P1 after age 50, and less so in P2/N1-P1. Furthermore, relative risk was unaffected by time or age. (Author abstract) (13 Refs)

4. PROGNOSTIC VALUE OF BONE MARROW BIOPSY IN BREAST CANCER.

Landys K
Dept. Radiotherapy, Jubileumskliniken, Sahlgrenska Sjukhuset, S-413 45 Goteborg, Sweden
Cancer; 49(3):513-518 1982

Bone marrow biopsies (BMB) were performed on 622 women with a history of primary or metastatic breast cancer. In 332 of the patients bone scintigraphy (BSC) was also carried out at the time of initial diagnosis or during follow-up. The BMB revealed metastases in 22/88 patients (25%) in Stage I-III with positive BSC and in 39/111 patients (35%) in Stage IV with positive BSC, a total of 61/199 patients (31%). Moreover, the BMB was positive in 6/73 patients in Stage I-III with negative BSC, and in 5/37 patients in Stage IV with negative BSC, a total of 11/110 patients (10%). Statistical evaluation showed that the patients with BMB revealing tumor had a significantly higher death risk (p less than 0.0000001) than patients with negative BMB. No significant correlation was found in patients with positive or negative BSC. Similar results were also found for a subgroup of 207 patients who underwent BSC and BMB within five months. BMB may therefore be indicated for verification of metastases and prediction of prognosis in all patients with positive BSC and in BSC-negative patients Stage II-IV. (Author abstract) (16 Refs)

5. HISTOLOGICAL DIFFERENTIATION AND PATTERNS OF METASTASIS IN BREAST CANCER (MEETING ABSTRACT).

Campbell FC, Blamey RW, Elston CW, Johnson J, Holliday HW, Doyle PJ
Nottingham City Hospital, Nottingham, England
Clin Oncol; 34(8):255 1981

Disseminated disease has so far developed in 168 of 550 patients who have undergone mastectomy for primary breast cancer. Tumors of 494 patients were graded histologically by two pathologists working independently who used a method similar to that of Bloom and Richardson (1957). Initial agreement was achieved in 90% of cases and a consensus decision was made on the remainder. Histological differentiation as assessed in three grades was found to correlate with distinct patterns of metastasis: (i) local recurrence to mastectomy flaps was not related to any histological grade; (ii) recurrence to regional lymph nodes requiring treatment was more frequent with poorly differentiated (grade III) tumors p less than 0.001. Grade III tumors have a higher overall incidence of distant recurrence and these tend to develop in viscera. Survival of patients whose initial distant metastasis occurred in viscera was poorer than that of patients whose first metastasis occurred in bone p less than 0.01. In summary, patients with poorly differentiated (grade III) cancers are likely to develop regional and distant metastases at an earlier stage than those with grade I or II tumors. Distant metastases in these patients are also more likely to develop in an unfavorable site with a poorer overall prognosis. (1 Ref)

6. HISTOLOGY AND CYTOMETRICS IN HUMAN BREAST CANCERS ASSAYED FOR THE PRESENCE OF PROLACTIN RECEPTORS.

Codegone ML, Di Carlo R, Muccioli G, Bussolati G

(c/o Bussolati), Istituto di Anatomia e Istologia Patologica, Via Santena 7, 10126 Torino, Italia

Tumori; 67(6):549-552 1981

Histology and cytometrics were evaluated in 50 cases of human breast infiltrating carcinomas (44 ductal, 6 lobular) assayed for the presence of prolactin receptors (PR). The tumors were considered PR positive when the level of specific binding reached or exceeded 0.5%. Twenty-six ductal infiltrating carcinomas and 4 lobular ones were PR positive. No strict correlation was found between PR and degree of histologic differentiation (expressed in grades) or menopausal status. Better differentiated (Grade I) ductal carcinomas were, however, mostly PR negative. Evaluation of the mean nuclear diameter (MND) and of the maximal epithelial cellularity (MEC) revealed that in ductal carcinomas a high level of PR (greater than 3% specific binding) was significantly correlated with a high MND. It is concluded that, contrary to that observed in estrogen receptor-positive tumors, PR-positive human ductal carcinomas are more likely to have large nuclei, ie, cytologically anaplastic, whereas better differentiated (Grade I) carcinomas are generally PR negative. (Author abstract) (15 Refs)

7. FURTHER EVALUATION BY ULTRASOUND OF MAMMOGRAPHICALLY DETERMINED BREAST DYSPLASIA.

Frazier TG, Cole-Beuglet C, Kurtz AB, Goldberg BB, Kvan SM

John S. Sharpe Res. Foundation, Bryn Mawr Hosp., Bryn Mawr, PA, 19010

J Surg Oncol; 19(2):69-70 1982

Evaluation of 135 consecutive patients was made for breast masses by the same surgeon and the patients were subsequently referred for ultrasound mammography of the breast afer xeromammography revealed a 'dysplastic' (DY) pattern only, with no evidence of malignancy. Three patients had carcinoma of the breast detected by ultrasound mammography that had been missed by xeromammography. Two of the three cancers were similarly diagnosed by fine-needle aspiration cytology. All patients with a normal ultrasound examination have now been followed for a minimum of 15 mo without evidence of developing breast cancer. This study confirms the importance of using additional diagnostic modalities for evaluating patients with dysplastic breasts and strongly suggests the value of ultrasound mammography in this group of patients. (Author abstract) (5 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

8. ESTROGEN RECEPTOR, A MARKER FOR HUMAN BREAST CANCER DIFFERENTIATION AND PATIENT PROGNOSIS.

Osborne CK, Fisher E, Redmond C, Knight WA, Yochmowitz MG, McGuire WL

Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284

Adv Exp Med Biol; 138:377-385 1982

Results in a group of patients undergoing mastectomy for primary breast cancer demonstrated that estrogen receptor (ER) may be a biochemical marker for tumor differentiation and is an important independent prognostic variable in such patients. Tumor differentiation and patient prognosis as functions of morphology, correlation of ER with nuclear and histologic grade, with tumor necrosis, elastica, and lymphocyte infiltration, and with prognostically unfavorable morphological characteristics are presented. Implications for therapy of primary breast cancer are discussed. (18 Refs)

9. BIOLOGIC MARKERS AND BREAST CANCER: A MULTIPARAMETRIC STUDY -1. INCREASED SERUM PROTEIN LEVELS.

Lamoureux G, Mandeville R, Poisson R, Legault-Poisson S, Jolicoeur R

Institut Armand-Frappier, Univ. Quebec, C.P. 100, Laval, Quebec H7V 1B7, Canada

Cancer; 49(3):502-512 1982

From early 1972 to the end of 1976, the profiles of several serum protein levels were used to monitor disease stage and prognosis of 207 patients with breast cancer. Six of these proteins, alpha 1-antitrypsin (alpha-AT), alpha 2-ceruloplasmin (Cp), beta 1-transferrin, IgA, C4, and C5, were significantly elevated in these cancer patients and were used as biologic markers in a multiparametric study. Among these breast cancer patients, 72% had at least two of these protein levels elevated, of which alpha-AT (55%), C5 (38%), and IgA (36%) levels were most commonly raised. The number of elevated proteins was parallel to disease progression as 61% (Group 1) and 74% (Group 2) of the patients with operable breast cancer and 90% of patients with metastatic disease showed an elevation of two or more of these nonspecific proteins. There was also a positive correlation between the number of elevated proteins and prognosis; of the 26 patients who died during the 5-year follow-up, only 4 (15%) had no more than one protein level elevated, and 22 (85%) had two or more protein levels elevated. On the other hand, when considered as a group, patients with no or only one protein level elevated had a better prognosis than patients with two or more levels elevated (p less than 0.03). This multiparametric study tends to indicate that the high level of these serum proteins, reflecting an abnormal biochemical profile, provides valuable information that relates to the stage of the disease and patients' prognosis. Results also suggest that these proteins may aid in differentiating the group with high recurrent risks from that with a more favorable prognosis for a given clinical and pathologic stage, illustrating their importance as biologic markers in breast cancer. (Author abstract) (58 Refs)

10. THE ROLE OF ESTROGEN RECEPTOR STATUS IN PREDICTING THE RESPONSE OF CARCINOMA OF THE BREAST TO ADJUVANT CHEMOTHERAPY.

Stephens RB, Abeloff MD, Mellits ED, Baker RR
Dept. Surgery, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD
Surg Gynecol Obstet; 154(2):200-204 1982

This study was undertaken to determine if there was any correlation between the estrogen receptor status and the response of patients with operable carcinoma of the breast to adjuvant chemotherapy. Seventy-seven patients with metastases to the axillary lymph nodes who were receiving adjuvant chemotherapy following a modified radical mastectomy were studied. During the period of study, 12 of 34 estrogen receptor-positive tumors recurred, with a mean disease-free interval of 17.8 mo, and 19 of 43 estrogen receptor-negative tumors recurred, with a disease-free interval of 15.2 mo. Statistical analysis of recurrence at 2 yr showed no difference between these two groups. Only one patient of 18 in the premenopausal group of women with estrogen receptor-positive tumors, however, had a recurrence compared with 11 of 24 patients with estrogen receptor-negative tumors. This difference was highly statistically significant (p greater than 0.0005). We have concluded that the estrogen receptor status is not a reliable indicator of response to adjuvant chemotherapy for all patients. Our data do indicate a positive correlation between response to adjuvant chemotherapy and estrogen receptor status in the premenopausal group of patients and suggest that adjuvant chemotherapy in the premenopausal group of patients may be exerting some of its effect by ovarian suppression rather than by a solely cytotoxic effect on cancer cells of the breast. (Author abstract) (8 Refs)

11. PROGNOSTIC VALUE OF THE ESTROGEN RECEPTOR LEVEL IN PATHOLOGIC STAGE I AND II ADENOCARCINOMA OF THE BREAST.

Shapiro CM, Schifeling D, Bitran JD, Desser RK, Rochman H, Michel A, Shapiro R, Evans R, Kozloff MF, Recant W, Billings AA
(c/o Bitran) Div. Hematology/Oncology, Michael Reese Hosp. and Medical Center, 29th St. and Ellis Ave., Chicago, IL, 60616
J Surg Oncol; 19(2):119-121 1982

The relationship between estrogen receptor levels and recurrence of breast cancer was examined in 302 patients with adenocarcinoma of the breast, pathologic Stage (PS) I and II. All 117 patients with PS II adenocarcinoma of the breast received adjunctive chemotherapy. In this series, there was no association between the estrogen receptor level and recurrence in either the 185 patients with PS I adenocarcinoma of the breast or the 117 patients with PS II adenocarcinoma of the breast. The most important prognostic variable was the presence or absence of axillary metastases. (Author abstract) (13 Refs)

12. RELATIONSHIP OF OESTROGEN RECEPTOR STATUS TO SURVIVAL IN EARLY BREAST CANCER (MEETING ABSTRACT).

Croton R, Cooke T, George WD, Nicholson K, Griffiths K
Department of Surgery, Royal Liverpool Hospital and Tenovus Institute, Liverpool, England
Clin Oncol; 34(8):254 1981

In early breast cancer, tumors without estrogen receptors recur earlier than tumors which are receptor positive. In the same way, survival in receptor negative cancer was reported to be decreased significantly in one group of patients. In this study 414 patients with early breast cancer were followed up for up to 4 yr. To date 50 deaths have occurred and the survival curves for subgroups of patients were compared by the log rank test. In the total group of 414 patients, those with receptor negative tumors had significantly decreased survival when compared to those with receptor positive cancers. This was true for both pre- and post-menopausal women. In patients with involved nodes, a similar trend was seen but this only just reached significance. For node negative tumors, those without receptors again showed a significantly decreased survival, and this group (node negative, ER negative) had a similar curve when compared with all the node positive patients. These results are similar to those reported for recurrence in an earlier study, and reinforce the importance of ER status as an independent prognostic indicator in breast cancer. (3 Refs)

13. ESTROGEN AND PROGESTERONE RECEPTORS AND RESPONSE TO AN ANTIESTROGEN OF POST-MENOPAUSAL ENDOMETRIAL CARCINOMA AND METASTATIC BREAST CANCER.

Baulieu EE, Mortel R, Levy C, Namer M, Robel P
Lab. Hormones, 94270 Bicetre, France
Excerpta Med Int Congr Ser; 551:234-245 1981

The effects of tamoxifen (TAM) on estradiol (ER) and progesterone receptor (PR) sites were measured in endometrial cancers and in skin metastases of breast cancers. In a group of 43 postmenopausal women with endometrial carcinoma, two biopsies from each were studied: at time of referral and during surgery or just prior to radiotherapy. Fifteen patients received TAM 40 mg/day po for 5-7 days after the first biopsy and the second biopsy was performed 12-18 hr after the last dose. Ten patients ingested 10 mg TAM 8 and 4 hr prior to the second biopsy. Total ER concentration (cytosol + nuclear) in tumors was similar to that in late proliferative phase of normal endometrium. Values for PR concentration were low and comparable to those found in the secretory phase of the normal menstrual cycle. No hormonal correlations of receptors was found. Where TAM immediately preceded biopsy, the ratio of cytoplasmic to nuclear receptor shifted in favor of nuclear receptors. In patients treated with TAM 12-18 hr before biopsy, PR sites increased in all but four samples, while in patients treated immediately before biopsy, no increase in PR was observed. TAM did not influence levels of ornithine decarboxylase or estradiol dehydrogenase. In a somewhat similar study in 21 women with advanced metastatic breast cancer, ER and PR were absent or low in 9; in 10/12 of the ER positive cases, only 2 were PR negative. There was a significant positive correlation between ER and PR in untreated tumors. After TAM administration, available ER sites were greatly decreased. No PR receptor change was observed where ER was less than 20 femtomole/mg cytosol protein. Among the remaining cases, 7/12 showed an increase of PR of greater than 100 femtomole/mg cytosol protein. (35 Refs)

14. RAPID ANALYSIS OF ESTROGEN AND PROGESTERONE RECEPTORS USING GEL-EXCLUSION HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY.

Pavlik EJ, Von Nagell JR, Muncey M, Donaldson ES, Hanson M, Kenady D, Rees ED, Talwalkar VR
Dept. Obstetrics and Gynecology, Univ. Kentucky, Albert B. Chandler Medical Center, Lexington, KY, 40536
Biochemistry; 21(1):139-145 1982

Estrogen and progesterone receptors prepared from mouse, rat, and human uteri, as well as from human breast cancers, have been characterized by gel-exclusion high-performance liquid chromatography. The qualitative relationships previously established by sedimentation analysis between the cytoplasmic [aggregated (approx 8S), deaggregated (approx 4S), and trypsinized (approx 3.6S)] and nuclear (approx 5S) forms of the rat uterine estrogen receptor were maintained by this technique. Differences in the partition of estrogen and progesterone receptors from the same species as well as interspecies differences in these receptors were reproducibly observed. Multiple forms of human estrogen and progesterone receptors could clearly be resolved in a single analysis and were distinct from serum steroid binding tissue contaminants. Separation analyses, performed at flow rates up to 2 mL min-1, were capable of resolving all receptor forms in 10-12 min with the column returning to base line in 25 min. With this exclusion gel column (TSK-G3000SW) as a background upon which to reference different receptor forms, eight distinct partitions or elution positions have been enumerated. This approach has considerable promise for the rapid characterization of different forms of steroid-receptor proteins. Moreover, it should provide a critical advantage in minimizing the opportunities for receptor modification during separation analysis and in maximizing the opportunity to study short-lived interactions between receptors and physiologic or pharmacologic ligands. (Author abstract) (37 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

15. PROGNOSTIC SIGNIFICANCE OF CEA IN BREAST CANCER: A STATISTICAL STUDY.

de Jong-Bakker M, Hart AA, Persijn JP, Cleton FJ
(c/o Persijn) Dept. Clinical Chemistry, Antoni van Leeuwenhoek-Huis/Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Eur J Cancer Clin Oncol; 17(12):1307-1313 1981

A statistical evaluation was carried out of serial CEA plasma levels in breast cancer patients. The study included 206 patients with operable primary tumor, 108 patients who were inoperable, 55 patients with advanced disease treated by oophorectomy and 77 post-menopausal patients treated with various endocrine regimens. The pretreatment CEA level was found to have no relation to prognosis. A rise in CEA during the follow-up period was usually associated with progressive disease. In 35% of the cases a rise in CEA preceded clinical signs of recurrence and metastases by an av of 200 deys. The practical value of CEA in the management of breast cancer is limited because many tumors do not produce CEA. In CEA-producing tumors it provides a useful aid in clinical evaluation. The need for a strict statistical evaluation of CEA data in the follow-up of breast cancer patients is stressed. (Author abstract) (18 Refs)

16. COMPARISON OF SERUM BLOCKING FACTORS ON LEUKOCYTE ADHERENCE INHIBITION AND PHA LYMPHOCYTE BLASTOGENESIS IN BREAST CANCER PATIENTS.

Fujisawa T, Yonemoto RH, Waldman SR
Dept. Surgery, Inst. Pulmonary Cancer Res., Chiba Univ. Sch. Medicine, 1-8-1, Inohana, Chiba 280, Japan
Jpn J Surg; 11(6):406-412 1981

Correlation between specific and nonspecific blocking factors, and tumor burden in patients with breast cancer (BC) were studied. Modified leukocyte adherence inhibition (LAI) assay and phytohemagglutinin-induced blastogenesis assay were used in the study. Serum blocking factors (SBF) in sera from 48 patients with BC were examined. Specific SBF in LAI assay were detected in 15/21 patients with recurrence, in 5/11 with local or regional involvement, and in 3/16 with no evidence of the disease (NED). Significant differences were found between patients with recurrence of the disease and patients with NED. SBF in LAI and lymphocyte blastogenesis (LB) correlated in 29/48 patients; 9/48 SBF positive in LAI and LB, 20/48 SBF negative in LAI and LB. SBF in LAI was demonstrated in 14/48 patients whose sera showed no SBF in LB. Results indicate that SBF in LAI and LB are either induced or derived from BC tissue. SBF in LAI correlates closely with the tumor burden. SBF in LB shows less correlation. LAI assay shows good potential use as routine clinical test for detection of cell-mediated immunity. SBF, directed to tumor-associated antigens, shows potential use for evaluation of immunocompetence, residuel tumor burden, and as a guide to therapeutic effects in cancer patients. (21 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

17. AMINOGLUTETHIMIDE AS TREATMENT OF POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CARCINOMA.

Santen RJ, Worgul TJ, Lipton A, Harvey H, Boucher A, Samojlik E, Wells SA
Milton S. Hershey Medical Center, Hershey, PA, 17033
Ann Intern Med; 96(1):94-101 1982

Hormone-dependent breast carcinomas respond to deprivation of biologically active estrogens with objectively quantifiable tumor regression. Aminoglutethimide, a known inhibitor of steroid synthesis, is also a potent blocker of the aromatase enzyme and, thus, of estrogen production. We develop an effective regimen to inhibit estrogen production in postmenopausal women using aminoglutethimide and replacement glucocorticoid. One hundred forty-seven women initially received aminoglutethimide and replacement glucocorticoid as treatment of metastatic breast carcinoma. One hundred twenty-nine women are currently evaluable for assessment of clinical and hormonal responses. Thirty-seven percent of unselected women and 49% of estrogen receptor-positive patients experienced objective tumor regression. Responses occurred predominantly in soft tissue (47%) and bone (35%) and lasted 30 +-9.1 mo for complete and 14 +-1.5 mo for partial regressions. Plasma and urinary estrogen levels fell equally in responder versus nonresponder groups whereas androgen levels declined less in patients with progressive disease. (Author abstract) (67 Refs)

18. DELAYED EFFECTS OF ADJUVANT CYTOTOXIC CHEMOTHERAPY ON THE LYMPHOID SYSTEM AND BONE MARROW IN STAGE II BREAST CANCER (MEETING ABSTRACT).

Mackay IR, Riglar C, Kitchen PR, Collins JP, Goodyear MD
No affiliation given
Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Thirty women with Stage II breast cancer given adjuvant cytotoxic chemotherapy for one yr with regimens including melphalan were studied to assess effects on bone marrow and immunological function, during and for up to three yr after cessation of therapy. There was long delayed recovery of blood cell numbers with leukocyte and platelet counts being significantly lower than pre-treatment values, even after three years. Correspondingly there was delayed recovery of counts in blood of T and B lymphocytes, but this was not reflected by functional tests relevant to the T cell system (delayed-type hypers ensitivity (DTH) responsiveness and mitogenic responsiveness to phytohemagglutinin) or the B cell system (levels of immunoglobulins and isohemagglutinins, and flagellin antibody responses). There was no evidence of drug-induced interference with natural killer (NK) or K cell function. Prediction of recurrence was not afforded by any of the immunological indices except DTH responsiveness but was afforded by slowly-progressive increases in serum levels of carcinoembryonic antigen. The possibility of prolonged, albeit mild, depression of hemo- and lymphopoiesis should be a consideration in the selection of types and duration of adjuvant chemotherapy regimens, and in the extension of such regimens to types and stages of cancer with a lower likelihood of mortality. (no Refs)

19. 2 N METHYL 9 HYDROXY-ELLIPTICINE IN TREATMENT OF METASTATIC BREAST CANCERS.

Rouesse J, Huertas D, Sancho-Garnier H, Le Chevalier T, Amiel JL, Brule G, Tursz T, Mondesir JM
Departement de Medecine Adulte, Institut Gustasve-Roussy, rue Camille-Desmoulins, F-94805 Villejuif Cedex, France
Bull Cancer (Paris); 68(5):437-441 1981

A phase II trial was conducted in 57 patients with advanced metastatic breast cancer given 2-N-methyl 9-hydroxy-ellipticine (NMHE) as 100 mg/m2 weekly. Evaluation of response, after at least four injections, was possible in 46 patients. Two complete regressions (of 3 and 12 mo) and seven regressions of over 50% were observed, a total regression rate of 19%. Regression was mainly observed in cutaneous or sc metastases. No objective regression was noted for pulmonary or hepatic metastases. Bone metastases were not taken into account when assessing response to treatment. Absence of hematological changes must be emphasized. The most frequent side effects were anorexia, nausea +- vomiting and dryness of mouth. Major toxicity was intravascular hemolysis, observed in 6 of 175 patients receiving NMHE in the Institut Gustave-Roussy, always controlled by symptomatic treatment. This product, of acceptable efficacy in breast cancer treatment, will probably occupy an original place in anti-cancer chemotherapy because of its lack of myelotoxicity. (Author abstract) (12 Refs) (In FRE)

20. TREATMENT OF ADVANCED BREAST CANCER WITH MEGESTROL ACETATE AFTER THERAPY WITH TAMOXIFEN.

Ross MB, Buzdar AU, Blumenschein GR
(c/o Buzdar) Medical Breast Service, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(3):413-417 1982

The efficacy of megestrol acetate in the treatment of advanced (Stage IV) carcinoma of the breast was studied in 48 evaluable patients who had been initially treated with tamoxifen. Forty-five patients had previously responded to the tamoxifen therapy. Fifteen patients (31%) had partial remission, 16 patients (33%) had stable disease, and 17 patients (36%) had progressive disease. The median respon se duration was 7 mo for responding patients and 6 mo for disease-stable patients. These results suggest that megestrol acetate is an effective agent for the palliation of advanced breast cancer relapsing following response to tamoxifen therapy. (Author abstract) (18 Refs)

21. 'EARLY' CARCINOMA OF THE BREAST: EVALUATION OF REGIONAL THERAPY AND FEATURES INFLUENCING PROGNOSIS.

Eilber FR, Milne CA, White EC, McBride CM
(c/o McBride) Dept. Surgery, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner St., Houston, TX, 77030
South Med J; 75(1):9-13 1982

Between 1944 and 1969, 192 women with carcinoma of the breast were treated at The University of Texas System Cancer Center M.D. Anderson Hospital and Tumor Institute by standard radical mastectomy for small outer quadrant lesions and pathologically negative axillary lymph nodes. Twenty percent of these patients with 'localized disease' eventually had disseminated breast cancer. Various patient, hormonal, genetic, and pathologic factors were found to have little influence on the prognosis. Patterns of metastatic disease revealed that these patients did not have a unique form of breast cancer, but apparently an earlier stage in the spectrum of advancing disease. The results of this study appear to represent the best that can be obtained with regional therapy for carcinoma of the breast and emphasize the need for reliable adjuvant therapy. (Author abstract) (16 Refs)

22. DELAYED RECOVERY OF PERIPHERAL BLOOD CELL NUMBERS AFTER ADJUVANT CYTOTOXIC CHEMOTHERAPY FOR STAGE II BREAST CANCER.

Goodyear MD, Mackay IR, Russell IS
(c/o Mackay) Dept. Medicine, Univ. Toronto, Princess Margaret Hosp. and Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Cancer Chemother Pharmacol; 7(1):37-40 1981

Thirty women were given chemotherapy (CT) following mastectomy for breast cancer with axillary lymph node metastases. Fourteen patients received melphalan (MP: 0.15 mg/kg/day for 6 days, repeated for 1 yr; the dose was later increased to 0.2 mg/kg/day). Sixteen patients received melphalan and methotrexate (MT: 0.2 mg/kg on day 8 of each cycle). Doses were adjusted according to test results. All patients were observed for 2 yr after the end of treatment. Tumors recurred in 12 patients, who were withdrawn from the study. Peripheral blood cell counts (PBCC) of leukocytes, neutrophils, lymphocytes, monocytes, and platelets showed no differences between treatment groups at any time. PBCC for patients prior to CT differed from PBCC for normal patients only in having a lower mean number of monocytes. Counts of all cell types declined progressively during the first 6 mo of CT. Counts rose after CT was stopped but 36 mo later had not reached pretreatment levels. Results indicate that administration of MP in patients following mastectomy produces depression of hemopoiesis and lymphopoiesis lasting up to 3 yr. Consideration of this depression is urged, particularly in cases of early breast cancer, when expectation of long-term survival is high. Monitoring of hematological function following CT is recommended to determine which CT regimens carry a risk of hematologic depression. (14 Refs)

23. A TRIAL OF ADJUVANT CHEMOTHERAPY IN OPERABLE BREAST CANCER (MEETING ABSTRACT).

George WD, Bush H, Howat J, Crowther D, Sellwood RA
Department of Surgery and Medical Oncology, University Hospital of South Manchester, Manchester, England
Clin Oncol; 34(8):256 1981

Because the early results of adjuvant chemotherapy in primary cancer of the breast were encouraging, a prospective randomized trial was established in 1976 to compare the two regimes reported to be of benefit with a no treatment group. Patients at high risk of early recurrence were randomly allocated after Patey mastectomy to receive either no further treatment, 12 courses of melphalan (L Pam) given six weekly, or 12 monthly courses of cyclophosphamide, methotrexate and 5 fluorouracil (CMF). To date 170 patients have been admitted. Fifty-five received no further treatment, 59 received L Pam and 56 CMF. The distribution by age, menopausal status, tumor size and number of involved nodes were similar in the three groups. Recurrence has occurred in 20 (36%) of the 55 controls, 19 (32%) of the 59 treated with L Pam and in 7 (12.5%) of the 56 who received CMF. Comparison of the three groups by life table analysis showed no difference in the rate of recurrence between the control and melphalan treated groups. Conversely the rate of recurrence in patients who received CMF was significantly lower than controls and this difference was true for both pre-menopausal and post-menopausal women. The results suggest that adjuvant melphalan confers no benefit after mastectomy, but that CMF may be effective in both pre- and post-menopausal women. (2 Refs)

24. CHEMOTHERAPY ASSOCIATING MITOMYCIN C, THIOTEPA AND VINDESINE IN ADVANCED BREAST CANCERS. STUDY OF 100 CASES.

Chauvergne J, Durand M, Burnet R, Bui BN, Hoerni B, Mauriac L
Fondation Bergonie, 180 rue de Saint-Genes, F-33076 Bordeaux Cedex, France
Bull Cancer (Paris); 68(5):442-448 1981

One hundred patients suffering from advanced breast cancers and resisting to one (15) or several (85) drugs previously administered have been treated by an association of mitomycin C, thiotepa and vindesine, given every 3 wk. Toxic effects were frequently observed and it was necessary to stop the treatment in more than 25% of the patients. Hemorrhagic complications due to thrombopenia (50% of cases) were severe in few cases and were responsible for the death of two patients. An overall objective response has been obtained in 41 cases and a regression in more than 50% of the lesions with a median duration of 7.5 mo has been observed in 15 cases. The most striking effects have been noted in lymph nodes and skin involvement with an appreciable effect on the functional (subjective) and painful syndrome in 60% of cases. Difficulties in applying this chemotherapy to patients who had already been heavily treated explain a toxicity which would probably be reduced by an earlier application of the treatment. The quality of the results obtained (here) with these patients incite to study the effect of this association primarily to improve the long-term prognosis of localized or already disseminated breast cancers. (Author abstract) (21 Refs) (In FRE)

25. ESTROGEN THERAPY AND BREAST CANCER - IS THE VERDICT IN?

Gambrell RD, Vasquez JM
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA
Contemp Obstet Gynecol; 19(1):38-45 1982

Risks involved in exogenous estrogen therapy are discussed. The incidence of breast cancer continues to rise steeply throughout the postmenopausal yr when estrogen levels have dropped. Prospective studies have given no evidence that estrogen replacement therapy for menopausal women increases the risk of breast cancer. Data indicate that estrogen, especially when combined with progestogen, may in fact be prophylactic. For women not treated with hormone replacement, a breast cancer incidence of 500/100,000 has been estimated. In women taking estrogens alone, an incidence rate of 137.3/100,000 has been obtained. In women treated with estrogens plus progestagens, the incidence rate is 95.6/100,000. Differences between estrogen users and untreated controls are statistically significant. Epidemiologic factors, the role of endogenous hormones, predisposing and protecting factors, and prognosis for breast cancer patients during estrogen therapy are discussed. (28 Refs)

26. TURISTERON: CLINICAL EXPERIENCE WITH A DEPOT ESTROGEN IN THE TREATMENT OF METASTATIC MAMMARY CARCINOMA.

Gurtler R, Tannenberger S, Bodek B, Morack G, Tannenberger S, Bodek B, Morack G
Zentralinstitut fur Krebsforschung der AdW, Lindenberger Weg 80, DDR-115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(2):129-139 1982

Sixty patients (54-86 yr old, av age 70 yr) in late menopause with metastatic mammary carcinoma were treated with the depot estrogen Turisteron. Forty-nine patients had undergone radical mastectomy; 2 had undergone simple mastectomy. Results in 51/60 patients were evaluable. Of these 51, 11 received 1 mg Turisteron/wk, po; 40 received 2 mg/wk. The lower dose was found to be unsatisfactory; a dose of 3 mg/wk was not tolerated well. Of the 40 patients receiving 2 mg/wk, 7.5% achieved complete remission with an av duration of 27 mo; 22.5% achieved partial remission with a 10 mo av duration, 10.0% showed clinical improvement, 32.5% showed tumor progress, 5.0% showed tumor stimulation, and 5.0% showed hypercalcemia. Results of therapy began to appear 4-6 wk after start of treatment. Turisteron was particularly effective against soft-tissue and lung metastases. Results indicate that Turisteron is suitable for treatment of metastatic mammary carcinoma during late menopause. Contraindications for treatment include cardiovascular disorders, liver damage, and hypercalcemia. Replacement of Turisteron therapy with cytostatic therapy if tumor stimulation occurs is recommended. (26 Refs) (In GER)

27. DRUG INTERACTION WITH ESTROGEN RECEPTORS FOR THE CONTROL OF BREAST NEOPLASIA (REVIEW).

Leclercq G, Heuson JC
Laboratiore et Clinique de Cancerologie mammaire, Service de Medicine, Institut J. Bordet, 1000 Brussels, Belgium
Anticancer Res; 1(4):217-228 1981

Major characteristics of most drugs that interact with estrogen receptors (ER) and are of potential value in treatment of breast cancers and other estrogen-sensitive neoplasias are reviewed. Drugs should present a maximal binding affinity for ER as well as minimal affinity for the non-receptor sites in order to be selectively taken up by the target tissues. Binding of estrogens and antiestrogens to ER depends on interaction with the hydrophobic pocket or the region binding the aminoalkyl side chain. Activity of the drugs depends on binding characteristics, effects on growth of human breast cancer cell lines, and in vivo properties. Triphenylethylene antiestrogens translocate cytoplasmic ER to the cell nucleus. Use of tamoxifen has been prompted by the lack of major side effects. Compounds with potential therapeutic value and active compounds of antiestrogens are presented. Estrogen-linked cytotoxic agents estradiol mustard and estracyt have been tested for treatment of advanced breast cancer; neither displayed significant binding affinity to ER. Antitumor activity of estrogens bearing a cytotoxic group or gamma-emitting radionuclide has not been confirmed, since ER can only be assessed by biochemical assays in tissue samples. A scintigraphic technique giving in vivo estrogen receptivity of a mammary cancer could provide valuable diagnostic and therapeutic information. (94 Refs)

REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT

28. PSYCHOIMMUNOENDOCRINE CHARACTERISTICS OF LONG SURVIVAL WITH BREAST CANCER (MEETING ABSTRACT).

Gorzynski JG, Holland J, Massie MJ, Katz J, Zumoff B, Fukushima D, Bekesi G
Memorial Sloan-Kettering Cancer Center, New York, NY
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

Ten yr ago 30 women were studied prior to breast biopsy for psychologic and endocrine state. They were studied for cortisol metabolite excretion rates, psychological defensive adequacy (using the Katz Defensive Adequacy Scale) and body wt. Following the biopsy, 22 women received the diagnosis of breast cancer, and 8 had benign disease. Ten yr later, 11 had died from breast cancer, and seven were located to participate in a follow up study of their psychoendocrine and immunologic state. Six of these women had negative nodal status; one had positive nodal status. Mean cortisol metabolite excretion rates, as determined prior to biopsy, were 5.9 mg/g creatinine for 7 surviving women and 4.3 mg/g creatinine for 11 women with breast cancer who died. Katz Defensive Adequacy Scale, as determined prior to biopsy, had a mean score of 2.7 for 11 women who died in the 10 yr period prior to follow up study and 6.3 for 7 surviving women (indicating greater failure of psychological defenses). Mean body wt at the time of biopsy was 142 pounds for 7 women who survived 10 yr and 179 pounds for those who died. Along with negative nodal status associated with long survival, these data suggest three additional psychoendocrine factors which contribute to long survival: lower body wt, greater psychologic defensive failure with greater emotional distress, and higher cortisol metabolite excretion rates. These findings suggest the need for further study of hypothalamic-pituitary-adrenal axis in women with breast cancer. (no Refs)

29. SUPPRESSED EMOTION IN WOMEN ATTENDING A BREAST SCREENING CLINIC (MEETING ABSTRACT).

Morris T
Faith Courtauld Unit for Human Studies in Cancer, King's College Hospital Medical School, London, SE5, England
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy. European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

As part of a series of studies on the psychological attributes of women who develop breast disease, all new white patients ages 25-69 attending a breast screening clinic during a calender yr were invited to complete the Eysenck Personality Questionnaire (EPQ), the Spielberger State-Trait-Anxiety Inventory (STAI), the Thomas Habits of Nervous Tension Scale and two scales on their reactions to and frequency of expression of anger. Eight cancer patients were excluded from the subsequent analysis. Eight hundred and two completed protocols were analyzed from 433 (54%) patients with benign breast disease and 369 (46%) without breast disease. Mean Scores for EPQ 'E' and 'N' were closely similar to Eysenck's norms for British women. EPQ 'L' and Spielberger A-State scores were slightly and significantly higher for women with benign breast disease than for those without breast disease. However, the mean A-Trait score at 40.25 and A-State mean at 40.13 indicated that as a whole, contrary to expectation, women attending the clinic were not unduly anxious. Among the patients studied, a small number only (20) displayed the pattern of response described in our studies of in-patients with breast cancer, that is low scores on anger ratings, low EPQ 'N' score, high EPC 'L' score, and very low A-Trait and A-State Scores. (no Refs)

30. THE BIOLOGICAL CORRELATES OF PSYCHOLOGICAL RESPONSES TO BREAST CANCER.

Pettingale KW, Philalithis A, Tee DE, Greer HS
The Faith Courtauld Unit for Human Studies in Cancer, King's Coll. Hosp. Medical Sch., Denmark Hill, London SE5, England
J Psychosom Res; 25(5):453-458 1981

Results of responses in breast cancer (BC) patients, correlations between biological measures, made pre-operatively and concurrently with the psychological assessment are presented and the implications are discussed. Sixty-nine consecutive women with BC were recruited to the study, 6 were excluded because they did not attend the follow-up examination and 1 because her psychological response was uncertain. No statistically significant associations were observed between the four psychological response groups (denial, fighting spirit, stoic acceptance, helpless/hopeless) and any of the various biological measures studied pre-operatively. At 3 mo post-operatively patients in the denial response group had significantly higher levels of serum IgM then either patients with a fighting spirit or stoic acceptance type of response. Patients in the fighting spirit group had significantly lower levels of serum IgM than patients who showed stoic acceptance. No statistically significant associations were observed between psychological response and lymphocyte transformation to phytohemagglutinin performed at 3 mo post-operatively. Mechanisms by which such immunoglobulin changes could influence survival in cancer remain hypothetical. A greater understanding of the neuroendocrine control of the immune system and much more sophisticated measurements are needed. (23 Refs)

31. THE ROLE OF THE RECTUS ABDOMINIS MYOCUTANEOUS FLAP IN BREAST RECONSTRUCTION.

Dinner MI, Labandter HP, Dowden RV

Dept. Plastic and Reconstructive Surgery, Cleveland Clinic Educational Foundation, 9500 Euclid Ave., Cleveland, OH, 44106

Plast Reconstr Surg; 69(2):209-214 1982

The rectus abdominis myocutaneous flap has been used in 10 patients requiring the importation of skin, sc tissue, and muscle for postmastectomy reconstruction. It was preferred to the latissimus dorsi myocutaneous flap under the circumstances. The flap has proved reliable and easy to raise, with a consistent anatomic location of the arterial venous pedicle. In 10 such flaps performed, one partial necrosis occurred in a patient who was extremely obese and had had a previous laparotomy that may have interfered with the integrity of the underlying blood supply to the rectus abdominis muscle. A minor complication of cellulitis in the donor-site wound was due to an idiosyncratic allergy to sutures used in the sc tissue. One instance of abdominal contour deformity was noticed in a patient in whom the anterior rectus sheath had been reconstituted by advancing the fascia of the external oblique muscle to meet the linea alba in the midline. In summary, we believe that the rectus abdominis myocutaneous flap, in certain select circumstances, produces a reliable, readily accessible myocutaneous flap to import tissue to the anterior chest wall for adequate mound reconstruction after mastectomy. Addendum: By the time of publication of this article, two patients have developed incisional hernias, which were probably related to technical error. (Author abstract) (6 Refs)

SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)

32. SPONTANEOUS REGRESSION OF BREAST CARCINOMA: FOLLOW-UP REPORT AND LITERATURE REVIEW.

Ross MB, Buzdar AU, Hortobagyi GN, Lukeman JM

(c/o Buzdar) Medical Breast Service, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030

J Surg Oncol; 19(1):22-24 1982

A case of spontaneous complete regression of metastatic breast carcinoma (malignant pleural effusion and bone metastases) was previously reported from M.D. Anderson Hospital and Tumor Institute. The patient did not receive any form of hormonal manipulation or systemic chemotherapy. This patient has now relapsed after 72 months of spontaneous complete remission, and a follow-up of her clinical history is presented. A search of the literature for previously reported instances of spontaneous regression of breast carcinoma indicates that this event is exceedingly rare. (Author abstract) (15 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

33. RELATIONSHIP OF WEIGHT TO THE PROMOTION OF BREAST CANCER AFTER MENOPAUSE.

de Waard F, Poortman J, Collette BJ

Dept. Epidemiology, Inst. Social Medicine, Utrecht, The Netherlands

Nutr Cancer; 2(4):237-240 1981

Epidemiologic and experimental evidence for a relation between high body wt and breast cancer is reviewed. A survey of the female population including 23,500 women 50 yr or older gave evidence for the initiation-promotion concept of breast cancer. Body wt and height were measured at each screening examination. Estrogen receptors (ER) were measured in 180/258 patients with breast cancer that was diagnosed during the survey. ER were found in 117 patients. The determination of ER-status of cancers has provided evidence that promotion in ER-positive cases is favored by obesity and inhibited by leanness. Estrogen-dependent breast cancer can be promoted by extra-ovarian estrogens from adipose tissue. The effect of wt and obesity is probably mediated through a menopausal estrogen mechanism. In lean postmenopausal women, clonal selection is thought to lead to a preponderance of ER-negative cells in cancer. Initiation of breast cancer is probably unrelated to obesity. Induction of breast cancer may be rare after menopause, but existing tumors grow if they receive stimuli to which they are sensitive. If wt reduction would prolong the free interval in breast cancer (until recurrence of secondaries), it would probably also be a means of controlling ER-positive breast cancer in its preclinical stages. (23 Refs)

34. EPIDEMIOLOGY OF BREAST CARCINOMA IV: AGE AND HISTOLOGIC TUMOR TYPE.

Rosen PP, Lesser ML, Senie RT, Duthie K

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

J Surg Oncol; 19(1):44-47 1982

The purpose of this study was to correlate major chronologic events known to have a bearing on the risk for developing breast carcinoma with histologic tumor type. Data were obtained for 1,024 consecutively treated patients with the seven most common forms of mammary carcinoma. The age of occurrence of the following events was determined: menarche; first marriage; first pregnancy and first childbirth; last pregnancy and last childbirth; diagnosis. The interval between each of these events and diagnosis of breast cancer was also calculated. Patients with medullary carcinoma had a significantly lower mean age at diagnosis than those with any of the other tumor types. Because of the lower mean age at diagnosis, medullary carcinoma patients were found to have significantly shorter intervals between age at diagnosis and the following: menarche, first pregnancy or first childbirth, and last pregnancy or last childbirth. Intervals between age at diagnosis and these other events were not significantly different among patients with other types of carcinoma. The ages of menarche, marriage, or pregnancy were not related independently to any tumor type. These data indicate that except for current age, the age of occurrence of major risk factors for developing breast cancer is unrelated to the histological type of tumor a patient develops. (Author abstract) (21 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

35. COMBINED EFFECTS OF 5-FLUOROURACIL (5FU) AND 2ALPHA DIMETHYLDEHYDROTESTOSTERONE PROPIONATE (2 ALPHA-MDTP) ON MCF-7 HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT).

Fujita H, Teller MN, Stock CC
Division of Chemotherapy, Keio University School of Medicine, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In vivo, the combination of 5-fluorouracil and 2 alpha dimethyldehydrotestosterone propionate treatment showed at least an additive effect on dimethylbenzanthracene (DMBA)-induced rat mammary tumors. To examine the evaluation of combined effects of 5 FU and 2 alpha-MDTP on MCF-7 human breast cancer cells, measurements were made on the inhibitory effects on cell proliferation and of the incorporation of 14C-thymidine, 14C-uridine and 14C-leucine into cellular DNA, RNA and protein. Combination of 5 FU and 2 alpha MDTP in concentrations tested gave enhanced inhibition of cell proliferation and of the incorporation of the precursors into cellular macromolecular substances as compared with treatment by each agent. This enhanced effect is additive. (no Refs)

36. ESTROGEN REGULATION OF GROWTH AND SPECIFIC PROTEIN SYNTHESIS IN HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

Edwards DP, AdamsDJ, McGuire WL
Dept. Medicine, Univ. Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX, 78284
Adv Exp Med Biol; 138:133-149 1982

New protein markers of estrogen action and dependence of progesterone receptors upon estrogen-stimulated cell growth were studied using MCF-7 human breast cancer cells in tissue culture. Results showed that estradiol stimulates DNA polymerase activity in normal target tissues. Progesterone receptor induction and estrogen-mediated cell division may involve separate control mechanisms. A specific 24,000 mol wt protein may be a marker of estrogen-stimulated growth of human breast tumor cells. (27 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abeloff MD	10
AdamsDJ	36
Albert S	3
Amiel JL	19
Baker RR	10
Baulieu EE	13
Bekesi G	28
Belle S	3
Billings AA	11
Bitran JD	11
Blamey RW	5
Blumenschein GR	20
Bodek B	26
Bodek B	26
Boucher A	17
Brule G	19
Bui BN	24
Burnet R	24
Bush H	23
Bussolati G	6
Buzdar AU	20
Buzdar AU	32
Campbell FC	5
Capdeville R	1
Chauvergne J	24
Cleton FJ	15
Codegone ML	6
Cole-Beuglet C	7
Collette BJ	33
Collins JP	18
Cooke T	12
Croton R	12
Crowther D	23
De Jong-Bakker	15
De Waard F	33
Dean P	2
Desser RK	11
Di Carlo R	6
Dinner MI	31
Donaldson ES	14
Dowden RV	31
Doyle PJ	5
Durand M	24
Duthie K	34
Edwards DP	36
Eilber FR	21
Elston CW	5
Evans R	11
Fisher E	8
Frazier TG	7
Fujisawa T	16
Fujita H	35
Fukushima D	28
Gambrell RD	25
George WD	12
George WD	23
Goldberg BB	7
Goodyear MD	18
Goodyear MD	22
Gorzynski JG	28
Greer HS	30
Griffiths K	12
Gurtler R	26
Hanson M	14
Hart AA	15
Harvey H	17
Hempelmann LH	2
Heuson JC	27
Hoerni B	24
Holland J	28
Holliday HW	5
Hortobagyi GN	32
Howat J	23
Huertas D	19
Janus J	2
Johnson J	5
Jolicoeur R	9
Katz J	28
Kenady D	14
Kitchen PR	18
Knight WA	8
Kozloff MF	11
Kurtz AB	7
Labandter HP	31
Lamoureux G	9
Landys K	4
Le Chevalier T	19
Leclercq G	27
Legault-Poisson	9
Lesser ML	34
Levy C	13
Lipton A	17
Logan W	2
Lukeman JM	32
Mackay IR	18
Mackay IR	22
Mandeville R	9
Massie MJ	28
Mauriac L	24
McBride CM	21
McGuire WL	36
McGuire WL	8
Mellits ED	10
Michel A	11
Milne CA	21
Mondesir JM	19
Morack G	26
Morack G	26
Morris T	29
Mortel R	13
Muccioli G	6
Muncey M	14
Namer M	13
Nicholson K	12
Osborne CK	8
Pavlik EJ	14
Persijn JP	15
Pettingale KW	30
Philalithis A	30
Poisson R	9
Poortman J	33
Recant W	11
Redmond C	8
Rees ED	14
Remy J	1
Riglar C	18
Robel P	13
Rochman H	11
Rosen PP	34
Ross MB	20
Ross MB	32
Rouesse J	19
Russell IS	22
Ryan SM	7
Salane M	3
Samojlik E	17
Sancho-Garnier	19
Santen RJ	17
Schifeling D	11
Sellwood RA	23
Senie RT	34
Shapiro CM	11
Shapiro R	11
Stephens RB	10
Stock CC	35
Talwalkar VR	14
Tannenberger S	26
Tannenberger S	26
Tee DE	30
Teller MN	35
Tursz T	19
Vasquez JM	25
Von Nagell JR	14
Waldman SR	16
Wells SA	17
White EC	21
Wolfe JN	3
Woodard ED	2
Worgul TJ	17
Yochmowitz MG	8
Yonemoto RH	16
Zumoff B	28

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)........ 1-2
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS........ 3-9
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS........ 10-14
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS........ 15-20
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)........ 21-28
- REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT........ 29-30
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY........ 31-32
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)........ 33-34

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BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. EFFECTIVENESS OF BREAST SELF-EXAMINATION TEACHING TO WOMEN OF LOW SOCIOECONOMIC CLASS.

McLendon MS, Fulk CH, Starnes DC
7532 Swan Run Road, Matthews, NC, 28105
JOGN Nurs; 11(1):7-10 1982

The effect of one-to-one teaching of breast self-examination (BSE) on the retention of knowledge and accuracy of performance was assessed in women of low socioeconomic class. One-hundred and eighty women were pretested, then 89 received one-to-one BSE instruction. The experimental group showed a significantly greater increase in knowledge from pretest to posttest than the control group and performed BSE with greater accuracy than the control group. This approach minimizes the cost of health care to this group of women. (11 Refs)

2. SELF-EXAMINATION AND SCREENING IN THE EARLY DIAGNOSIS OF BREAST CANCER.

Battersby C
Dept. Surgery, Royal Brisbane Hosp., Brisbane, Australia
Cancer Forum; 5(4):196-200 1981

Interest in breast self-examination (BSE), campaigns, influence of BSE on results and early diagnosis, why BSE is avoided and what can be done, role of the doctor in BSE, and screening of the total population for breast cancer (medical examination, breast imaging, and screening for asymptomatic patients) are discussed. Most breast lumps are discovered by women themselves. Lumps smaller than 1 cm can be detected by BSE when node involvement is uncommon and 80-90% 10-yr survival occurs. BSE is the cheapest way of screening for breast cancer. Recommendations for screening high- and low-risk women are made. (11 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

3. ULTRASONIC APPEARANCE OF MAMMARY CARCINOMA WITH A DEDICATED WHOLE-BREAST SCANNER.

Maturo VG, Zusmer NR, Gilson AJ, Bear B
Ultrasound Section, Baumritter Inst. Nuclear Medicine, Mt. Sinai Medical Center, 4300 Alton Road, Miami Beach, FL, 33140
Radiology; 142(3):713-718 1982

Forty-four pathologically proved mammary carcinomas were studied by clinical examination, xeroradiography, and ultrasonography with a dedicated whole-breast scanner. Abnormalities reflecting carcinoma were shown by echography in 90% of cases and xeromammography in 97%. Ultrasonic manifestations of malignancy were separated into four categories: (a) a solid, hypoechoic mass; (b) a hyperechoic focus: (c) an irregular, echogenic zone of parenchymal disruption; and (d) an atypical cystic mass. Dedicated ultrasound instruments enhance interpretation and improve differential diagnostic capability. Sonography demonstrates abnormalities better and permits superior definition of abnormal characteristics in a dysplastic breast than in a fatty, atrophic breast, while xeromammography may be more reliable in postmenopausal women with fatty breasts than in women with mammographically dense breasts. One limitation of current ultrasound equipment is the inability to consistently demonstrate microcalcification. (Author abstract) (20 Refs)

4. INTEROBSERVER VARIATION IN THE IDENTIFICATION OF BREAST CARCINOMA IN INTRAMAMMARY LYMPHATICS.

Gilchrist KW, Gould VE, Hirschl S, Imbriglia JE, Patchefsky AS, Penner DW, Pickren J, Schwartz IS, Wheeler JE, Barnes JM, Mansour EG
Pathology Coordinating Office, Eastern Cooperative Oncology Group, Medical Science Center, Room 4760A, 420 N. Charter St., Madison, WI, 53706
Hum Pathol; 13(2):170-172 1982

Nine surgical pathologists participated in a microscopic review of 35 cases of pT1-2 N0 M0 breast carcinoma. The pathologists outlined strict criteria for the identification of intramammary lymphatics and blood vessels and for the identification of cancerous emboli in these vascular channels. Each mastectomy case was studied by three different pathologists. All three concurred on the presence or absence of intralymphatic cancer in 12 of the 35 cases. Observers agreed on the absence of blood vessel invasion in 30 of the 35 cases. There was no consistent bias on the part of a single reviewer, either alone or with another pathologist, in identifying the emboli. We conclude that the identification of intralymphatic cancerous emboli in mastectomy specimens is not a reliably reproducible prognostic finding on which recommendation of systemic chemotherapy in Stage I breast carcinoma patients can be based. (Author abstract) (9 Refs)

5. MAST CELLS IN THE AXILLARY NODES OF BREAST CANCER PATIENTS.

Thoresen S, Tangen M, Hartveit F
The Gade Inst., Dept. Pathology, Haukeland Hosp., Univ. Bergen, Bergen, Norway
Diagn Histopathol; 5(1):65-67 1982

Mast cell counts were undertaken in histological samples from 64 cases of infiltrating breast cancer which had been divided into three groups: no metastases found in any nodes examined, some but not all nodes containing metastases, or all nodes containing metastases. An association was evident between the mast cell content per unit area and the presence of metastatic tumor in the axilla. An/increase in mast cell content in patients with metastases was seen in cortex, paracortex, and medulla, but the highest values were observed in the paracortex. (13 Refs)

6. CYTOLOGIC STUDIES OF NIPPLE DISCHARGES.

Takeda T, Suzuki M, Sato Y, Hase T
Dept. Internal Medicine, Miyagiken Seijinbyo Center, Natori City, Miyagi-ken 981-12, Japan
Acta Cytol (Baltimore); 26(1):35-36 1982

Cytologic findings of nipple discharges from 71 histologically confirmed breast cases (29 malignant and 42 benign) were analyzed. Papillary clusters composed of more than 30 ductal cells were found in the discharges from 18 of the malignant cases (62%) and 6 of the benign cases (14%); all 6 benign cases with papillary clusters were papillomas. Erythrocytes were detected in the discharges from 15 of the malignant cases (52%) and 5 of the benign cases (12%); 4 of the 5 benign cases with bloody discharge were papillomas. Both erythrocytes and papillary clusters were observed in the discharges from 14 of the malignant cases (48%) and 2 of the benign cases (5%). (Author abstract) (5 Refs)

7. THE VALUE OF PROGNOSTIC PARAMETERS FOR THE STRATIFICATION OF ADVANCED BREAST CANCER PATIENTS.

Morz R, Francesconi M, Schemper M, Rainer H, Jakesz J, Moser K
Dept. Medicine 1, Univ. Vienna, Lazarettgasse 14, A-1090 Vienna, Austria
J Cancer Res Clin Oncol; 102(3):289-299 1982

One hundred seventy-five patients with metastatic breast cancer, treated with a combination chemotherapy (Cooper regimen), were analyzed retrospectively to identify the value of the traditional prognostic parameters (disease-free interval; menopausal status; dominant site of metastatic lesion) for the stratification of patients before randomization. Response rate and survival time were not significantly affected by the disease-free interval and menopausal status. A significant difference was detected among the three categories of dominant disease (locoregional; osseous; visceral). However, an estimate of total extent of disease (according to Swenerton) was found to be the most important factor for predicting response and survival time after combination cytotoxic treatment. The differences between the dominant size of metastatic disease are mainly influenced by different size of metastatic spread. Therefore, there is found a significant correlation between the different types of dominant lesions and total extent of disease. In conclusion, the particular sites of metastatic spread seem to be of less importance than overall extent of disease in predicting the outcome. A critical evaluation of the three traditional stratification parameters and introduction of a semiquantitative estimation of total tumor burden as a new stratification parameter seems to be necessary when planning and comparing future trials. (Author abstract) (26 Refs)

8. DISEASE AND SECOND DISEASE TABLES FOR MAMMARY CARCINOMA.

Schicke B, Baldauf K, Zur Horst-Meyer
Organisations- und Rechenzentrum des Stadtischen Klinikums Berlin-Buch, Wiltbergstr. 50, DDR-1115 Berlin, E. Germany
Radiobiol Radiother (Berl); 22(6):755-758 1981

The probabilities of first and second occurrences of breast cancer were studied. Probability tables were constructed for 5-yr age groups in the age range 15-85 yr. The occurrence of a second mammary carcinoma was studied in 4562 cases involving a successfully treated first mammary carcinoma. The occurrence rate for this group was 2.5x of the expected rate. Results indicate that postoperative monitoring of mammary carcinoma patients should continue for the rest of the patient's life, rather than ending after 5 yr. (6 Refs) (In GER)

9. BREAST MASSES IN ADOLESCENT FEMALES.

Goldstein DP, Miler V
Div. Gynecology, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA, 02115
Clin Pediatr (Phila); 21(1):17-19 1982

The clinical records of 51 female patients between the ages of 8 and 20 years who underwent excision of breast masses at Boston's Children's Hospital Medical Center were reviewed. In most instances excisional biopsy using local or general anesthesia was performed on an ambulatory basis. Fibroadenomas account for the majority of breast masses (81.4%). There were no malignancies. Breast tumors in pediatric and adolescent populations are best managed by careful physical examination, careful follow-up, needle aspiration when feasible, observation and surgical excision of persistent, enlarging or symptomatic masses. Patient education and breast self-examination teaching are highly recommended. Excisional biopsy of unilateral subareolar masses in the early pubertal female should be avoided, since these usually represent a physiologically enlarged breast bud. (Author abstract) (8 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

10. OESTROGEN AND PROGESTERONE CYTOSOLIC RECEPTORS IN CLINICALLY INFLAMMATORY TUMOURS OF THE HUMAN BREAST.

Delarue JC, May-Levin F, Mouriesse H, Contesso G, Sancho-Garnier H
Unite de Biochemie Hormonale, Institut Gustav-Roussy, 94800 Villejuif, France
Br J Cancer; 44(6):911-916 1981

Estrogen (RE) and progesterone (RP) cytosolic receptors have been studied in 59 clinically inflammatory tumors of the human breast. The results were compared to those obtained in a series of 496 operable tumors. A single saturating dose of estradiol for RE and R5020 for RP was used and the cut-off between negative and positive tumors was 100 fmol/g tissue. A significant difference was seen (p less than 0.02) between the two classes of patients: (RE-, RP-) tumors were commoner among clinically inflammatory tumors (48%) than among operable ones (28%), independently of menopause. Concerning the histological type (based on an assessment of differentiation) and the histological grading there was a significant difference (p less than 0.001) between the two populations of tumors. No significant differences was found in the distribution of RE and RP among the three histological types, whereas a significant correlation existed between histological grading and RE (p less than 0.02). Finally, patients with RE clinically inflammatory tumors constitute a lower risk group, especially when they are free of metastases at the time of diagnosis. The presence of RE therefore seems to indicate, as in the operable tumor group, a favorable prognosis. (Author abstract) (34 Refs)

11. STEROID RECEPTORS IN EARLY BREAST CANCER: VALUE IN PROGNOSIS.

Nicholson RI, Campbell FC, Blamey RW, Elston CW, George D, Griffiths K
Tenovus Inst. Cancer Res., Cardiff, Wales
J Steroid Biochem; 15:193-199 1981

The relationship of prognosis to estradiol-17 beta receptor (ER)-status of prima ry breast tumors was studied in 550 patients who presented consecutively to one surgeon (Group A) and in 421 patients dealt with by 15 surgeons (Group B). Systemic treatment of patients after mastectomy was withheld until recurrence of disease. Clinical staging of Group A was by node involvement, and Group B by the international TNM system. Data from both groups indicate no relationship between ER-status and the stage of the disease, nor with tumor size. No advantage is evident by considering the quantity of receptor in the primary tumor since the correlations are not sufficiently strong to allow the prediction of recurrence to be accurately assessed for an individual patient. Group A patients with nodal involvement and ER-positive tumors have, as a group, a more favorable prognosis, approx 70% surviving 3 yr. Node positive ER-positive patients with grade I and II tumors have a good prognosis and do as well as patients without nodal involvement. Tumors with measurable receptor levels were found in 219 patients of Group B. A group of 116 patients without nodal involvement but with ER-negative tumors, despite favorable prognosis, unexpectedly recurred at the same rate as all women with axillary node involvement. Generally the rate of survival was significantly longer in patients with ER-positive tumors. In Group A major local recurrence occurred in 82 patients of whom 42 developed distant metastases and a further 82 had clinical evidence of distant metastases without prior local recurrence. ER-status did not relate to local recurrence, nor to the incidence of 'spot' recurrence. Thirty-one percent of Group A patients with ER-positive primary tumors treated with endocrine therapy responded, while only 5% of the ER-negative tumors were confirmed as responders by external assessment. (30 Refs)

12. STEROID RECEPTORS IN BREAST CANCER.

Cowan K, Lippman M
Medical Breast Cancer Section, Medicine Branch, NCI, NIH, Building 10, Room 6B02, Bethesda, MD, 20205
Arch Intern Med; 142(2):363-366 1982

Progress in hormone action mechanisms, analysis of estrogen receptors (ER) and progesterone receptors (PR), ER and disease-free interval, and ER and response to cytotoxic chemotherapy (CCT) are reviewed. According to the current hypothesis regarding mechanisms of action, circulating steroid hormones are first taken up by target cells and subsequently bind to specific cytoplasmic receptor molecules. New protein synthesis that occurs in hormone-responsive cells results in changes in the cell phenotype. Reasons for the lack of a perfect correlation between ER status and response to endocrine therapy are the instability of steroid receptors, heterogeneity of malignant cells, existence of numerous endocrine therapies that are ablative and additive, hormone-dependent and independent tumor cells, and the possibility of primarily nuclear location of ER sites and their undetectability in routine assays of cytoplasmic receptors. Patients with tumors that contain both ER and PR have the highest frequency of response (75-80%) to endocrine therapy. Explanations for apparent lack of complete correlation between the presence of PR and response to hormonal therapy are that the biopsy specimens were obtained during the luteal phase of the menstrual cycle and that some postmenopausal patients may actually have concentrations of endogenous estrogen that are insufficient to induce detectable increments of tumor PR activity. ER determination could aid in the selection of a subgroup of women with stage I primary breast cancer who might benefit from early aggressive adjuvant therapy. A definite role of ER status in selection of patients for CCT has not been established. (34 Refs)

13. IS A FUNCTIONAL ESTROGEN RECEPTOR ALWAYS REQUIRED FOR PROGESTERONE RECEPTOR INDUCTION IN BREAST CANCER?

Horwitz KB
Dept. Medicine and Biochemistry, Univ. Colorado, Health Science Center, Denver, CO, 80262
J Steroid Biochem; 15:209-217 1981

Presence of a functional estrogen receptor (ER) as a requirement for progesterone receptor (PR) induction in breast cancer (BC) was studied in the T47D human BC cell line. ER and PR were measured after 30 passages in modified medium. Cells had less than 0.04 picomole/mg DNA of specific, unfilled ER in the cytoplasm when measured on a sucrose gradient. ER are anomalous: 10 nanoM estradiol treatment failed to deplete and translocate cytoplasmic receptors, and nuclear receptors failed to be subsequently processed. ER of T47D cells also have an unusual response to the estrogen antagonist, nafoxidine, cell growth is not inhibited and minimal effects on PR were observed. PR are heat labile, sediment at 7-8S on sucrose gradients, and specifically bind progestins. After 0.1 uM progesterone treatment (PT) PR rapidly (1-2 min) move out of the cytoplasm and into the nuclei. One hr of PT depleted PR, and these were fully restored in 10-24 hr when progesterone was removed, indicating that the cells are either functionally ER-negative, or the ER are in a permanently activated state in the nucleus. Nafoxidine reverses this activated processed state. After 4 days on 20 ug/ml B-bromodeoxyuridine PR levels were reduced 70%. This effect was completely prevented by addition of excess thymidine (10x). When T47D cells were cultured in the presence of 10 milliM butyrate, PR levels fell 32% in 24 hr, and 55% in 36 hr. The inhibitory effect was completely reversible even after 72 hr, if the compound was removed from the medium. Results suggest that transcription of the PR gene in T47D cells is not constitutive, but remains at least partially regulated. (30 Refs)

14. EXPRESSION OF MULTIMOLECULAR FORMS OF PYRUVATE KINASE IN NORMAL, BENIGN, AND MALIGNANT HUMAN BREAST TISSUE.

Ibsen KH, Orlando RA, Garratt KN, Hernandez AM, Giorlando S, Nungaray G

Dept. Biological Chemistry, California Coll. Medicine, Univ. California, Irvine, CA, 92717

Cancer Res; 42(3):888-892 1982

The levels of multimolecular forms of pyruvate kinase present in four normal human breast specimens, nine benign tissues, and 13 malignant breast carcinomas were determined. The different enzymatic forms were separated by isoelectrofocusing, quantitated photometrically, and characterized further by kinetic studies using phosphoenolpyruvate as the variable substrate in the presence of different effectors. A correlation between specific activity and malignancy was found. The mean specific activities (- S E) of the normal, benign, and malignant tissues were: 0.078 -0.006, 0.36 -0.072, and 3.50 -0.696 IU/mg protein, respectively. A form of pyruvate kinase with an isoelectric point (pI) of 7.0 predominated in the breast tissues. The properties of this form were consistent with it being the K4 isozyme, known to be widely distributed in mammalian tissues. Higher pI forms were also found. The M4 isozyme, expressed by normal muscle and brain, has a pI value similar to the highest pI form found in the breast tissues. Therefore, the pI data alone suggest that the breast specimens also express some M-type subunits. This conclusion was not supported by the kinetic data. The higher pI forms are thought to be a posttranslationally modified K isozyme. Although this modified form is found in normal specimens, it seems more prevalent in neoplasms. (Author abstract) (19 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

15. THE LAI TEST AND THE GRAPHICAL FOLLOW-UP TECHNIQUE OF POST SURGICAL BREAST CANCER UNDER LEVAMISOLE TREATMENT.

De Carli HO, Restberg V
Hospital San Roque, C. C. 350, Gonnet, 1900 La Plata, Argentina
Quiron; 12(3/4):3-14 1981

The leukocyte adherence inhibition (LAI) test was used to evaluate breast cancer patients preoperatively and at various times postoperatively. The nonadherence index (NAI) was calculated: values greater than 30% were considered positive and those less than 30% negative. In most presurgical patients, NAI was positive (mean 104 -75%), and the LAI test confirmed the microscopic diagnosis in greater than 90% of cases. Mean NAI values obtained 1 mo-5 yr after surgery diminished to 68 -49%, although the difference was not statistically significant. Comparison of the NAI values for presurgical patients with those of postsurgical patients obtained up to 4 mo after surgery revealed a significant difference. Levamisoles (LEV: 50 mg 3x/wk for 3-wk periods) significantly decreased the mean NAI (11 -41%) compared with values of patients not given the drug. The mean NAI of patients with metastases was-21 -35%. Differentiation of ductal and lobular breast cancer was not possible with the LAI test. Correlation between the LAI test and dinitrochlorobenzene skin testing was difficult. LAI negative patients with residual tumors may become LAI positive after several courses of LEV, and may then become negative after the therapeutic action of LEV takes effect. (12 Refs)

16. PROSPECTIVE EVALUATION OF THE LEUKOCYTE ADHERENCE INHIBITION (LAI) TEST IN BREAST CANCER USING A PANEL OF EXTRACTS FROM KNOWN AND UNKNOWN PRIMARY TUMORS.

Fritze D, Kaufmann M
Medizinische Universitatsklinik, D-69 Heidelberg, W. Germany
Int J Cancer; 29(3):261-264 1982

The antigen-induced leukocyte adherence inhibition (LAI) test is an assay of cellular immune reactivity which was expected to offer a promising adjunct to currently available diagnostic and monitoring procedures in cancer patients. We have applied this assay to 83 inpatients clinically suspected of having breast cancer, 50 outpatients before mammography, and 37 healthy women. In order to account for the known heterogenicity of breast cancer, we performed LAI assays with extracts from 15 primary tumors of known and 14 primary tumors of initially unknown histology. Thus, the problem of tumor specificity in the LAI assay was tackled in a double-blind fashion. The results obtained clearly show that breast-tissue-specific rather than tumor-specific responses were detected by LAI testing. The LAI assay failed to discriminate between high-risk patients with and without cancer and between extracts from breast tumors with and without carcinoma. The results are discussed with regard to the many claims for the detection of specific tumor immunity in the literature. (Author abstract) (25 Refs)

17. QUANTITATION OF RESPONSE TO THERAPY IN PATIENTS WITH METASTATIC BREAST CARCINOMA BY SERIAL ANALYSIS OF PLASMA GROSS CYSTIC DISEASE FLUID PROTEIN AND CARCINOEMBRYONIC ANTIGEN.

Silva JS, Leight GS, Haagensen DE, Tallos PB, Cox EB, Dilley WG, Wells SA
Sloan-Kettering Memorial Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 49(6):1236-1242 1982

The maximum percent change (MPC) of plasma carcinoembryonic antigen (CEA) and gross cystic disease fluid protein (CDP) were correlated with response to therapy in 92 metastatic breast carcinoma patients. In patients treated with hormone therapy MPC values were significantly different between patients with disease progression (Prog) and regression (Reg): MPC-CEA for Reg = 72 -7%, for Prog = 396 -150%; MPC-CDP for Reg =-86 -6%, for Prog = 702 -330%, p less than 0.001 in a one-way ANOVA for CEA and CDP. Similar differences were noted in patients treated with chemotherapy. Decreased (greater than 50%) plasma CEA levels were observed in 24/29 (83%) of Reg, 18/35 (51%) stable and 0/49 (0%) of Prog; decreased (greater than 50%) plasma CDP levels were noted in 19/24 (79%) of Reg, 21/28 (75%) of stable and 2/35 (6%) of Prog. Patients with plasma marker decreases greater than 50% had significantly longer responses to therapy (14.2 mo for CEA, 14.1 mo for CDP) compared to patients with less than 20% decrease (2.0 mo for CEA, 0.8 mo for CDP), p less than 0.001 in a one-way ANOVA. Decreasing marker levels during the initial 6 wk of therapy (negative slope) accurately identified Reg or stable patients: the predictive value of a negative slope was 92% for CEA and 86% for CDP. Rising marker values correctly identified treatment failures (Prog): the predictive value of a positive slope was 90% for CEA and 76% for CDP. These data indicated that changes in plasma CEA and CDP levels reflected increasing or decreasing tumor burden during hormone or chemotherapy treatment of metastatic breast carcinoma. Criteria have been established to predict therapeutic outcome based on the slope of CEA or CDP after 6 wk of treatment. (Author abstract) (25 Refs)

18. IMMUNOCYTOCHEMICAL DETECTION OF TUMOUR MARKERS IN BONE METASTASES FROM CARCINOMA OF THE BREAST.

Gugliotta P, Botta G, Bussolati G
Istituto di Anatomia e Istologia Patologica, Univ. Turin, Turin, Italy
Histochem J; 13(6):953-959 1981

Immunocytochemical methods were employed for the detection of seven tumor-associated antigens in 10 cases of bone metastases from carcinoma of the breast. The biopsy specimens were fixed and decalcified in Bouin's soln using an apparatus which utilized ion-exchange resins. The following antisera were employed: anti-milk fat globule membrane (MFGM), anti-carcinoembryonic antigen (CEA), anti-human beta-casein, anti-human alpha-lactalbumin, anti-human chorionic gonadotropin (alpha subunit), anti-pregnancy-specific beta-1-glycoprotein, and anti-human placental lactogen. Application of immunoperoxidase methods to bone marrow was only possible after inhibition of endogenous peroxidase activity with periodic acid. With anti-MFGM serum metastatic neoplastic cells were detectable in all cases; the percentage of positive cells varied from case to case. CEA was detected in 9/10 cases. Casein was detected in only five cases; all other antisera were essentially negative. Most of the 10 cases of primary breast cancer were positive for MFGM, CEA, and casein; all were negative for lactalbumin and only one or two showed some neoplastic cells positive for at least one of the placental antigens. Therefore, MFGM and CEA appear to be the most useful markers for the identification of metastatic neoplastic cells in bone marrow originating from cancers of the breast. (23 Refs)

19. MONOCLONAL ANTIBODIES TO THE HUMAN MAMMARY GLAND. I. DISTRIBUTION OF DETERMINANTS IN NON-NEOPLASTIC MAMMARY AND EXTRA MAMMARY TISSUES.

Foster CS, Edwards PA, Dinsdale EA, Neville AM
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 GPX, England
Virchows Arch [Pathol Anat]; 394(3):279-293 1982

Mouse monoclonal antibodies have been raised to the human milk fat globule membrane. The distribution of the antigens detected by four of the antibodies has been examined in formalin-fixed, paraffin-embedded human tissues by light microscopic immunocytochemistry. The four antibodies stain lactating breast and normal resting breast. Two exclusively stain the luminal membranes of breast epithelial cells. A third antibody stains in addition the lateral membranes of duct epithelial cells. The fourth antibody stains both epithelial and myoepithelial cells. None of the antibodies is breast specific, nor do they stain every epithelial cell within the breast. Instead, each antibody reveals a complex and heterogeneous distribution of staining throughout the normal tissues. Within the breast, the staining by a given antibody is usually segmental and conforms to secretory units and their associated ducts. Similarly heterogeneous patterns of staining are also observed in the extramammary normal tissues. Despite the apparent morphological identity between breast epithelial cells when examined by conventional light microscopy, the hitherto unrecognized 'functional' heterogeneity, which as been revealed by the monoclonal antibodies could have importance in understanding the biology of the normal breast and the pathology of breast cancer. (Author abstract) (18 Refs)

20. MONOCLONAL ANTIBODIES TO THE HUMAN MAMMARY GLAND. II. DISTRIBUTION OF DETERMINANTS IN BREAST CARCINOMAS.

Foster CS, Dinsdale EA, Edwards PA, Neville AM
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Virchows Arch [Pathol Anat]; 394(3):295-305 1982

A range of primary and metastatic human breast carcinomas has been examined with respect to the staining by four monoclonal antibodies which were raised to the human milk fat globule membrane. Within the normal breast the luminal epithelial cells expressing the antigens detected by the monoclonal antibodies were heterogeneous in their distribution. The heterogeneity was not only confined to single cells, but also to regions within the breast. The breast carcinomas also expressed the antigens in a variable manner. Morphological differentiation and functional differentiation, defined by the monoclonal antibodies, were not invariably coincident. Lymph node metastases gave similar results to the primary carcinomas. The monoclonal antibodies have revealed a heterogeneity, with respect to surface antigenic expression, within the normal and neoplastic breast epithelium. This cellular heterogeneity of breast carcinomas, may have significant prognostic and therapeutic implications in the management of primary breast cancer. (Author abs tract) (17 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

21. MULTICENTRIC BREAST CARCINOMAS: CLINICAL-RADIOGRAPHIC-PATHOLOGIC WHOLE ORGAN STUDIES AND 10-YEAR SURVIVAL.

Egan RL
Mammography Section, Emory Univ. Clinic, 1365 Clifton Road, NE, Atlanta, GA, 30322
Cancer; 49(6):1123-1130 1982

Selection of breast cancer patients with microscopically limited disease but with excess mortality or women with regional disease and lessened mortality has remained an unsolved and critical challenge. The many usual histologic features such as tumor size, stage of disease or tumor differentiations were found reduced to lessened significant prognostic factors by the presence of multicentricity of tumor and multiplicity of histologic types of carcinoma. This observation was noted upon review of 161 clinical, radiographic and histopathologic whole breast studies on 156 patients with follow-up from 11-15 yr. Epidemiologic, clinical, and radiographic data had been compiled prospectively prior to diagnosis. Women with a single site and single type of carcinoma had a better prognosis (2.5% mortality per yr) than those with multiple sites and multiple types (15% mortality per yr) even though the stage of the disease may be similar. When the latter groups contained a scirrhous type duct carcinoma, the annual mortality rate approached 25%. (Author abstract) (34 Refs)

22. PROLONGED DISEASE-FREE SURVIVAL IN ADVANCED BREAST CANCER TREATED WITH 'SUPER-CMF' ADRIAMYCIN: AN ALTERNATING REGIMEN EMPLOYING HIGH-DOSE METHOTREXATE WITH CITROVORUM FACTOR RESCUE.

Henderson IC, Gelman R, Canellos GP, Frei E
Div. Medical Oncology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer Treat Rep; 65(Suppl1):67-75 1981

Sixty-six patients were treated with the combination 'super-CMF' as follows: cyclophosphamide 100 mg/m2 po days 1 through 14; methotrexate 3.0 g/m2 iv days 1 and 8; 5-fluorouracil 600 mg/m2 iv days 1 and 8; citrovorum factor rescue 10 mg/m2 days 2 and 9 and po days 2 through 4 and 9 through 11; and adriamycin 70 to 90 mg/m2 iv day 29. This cycle was repeated at 49-day intervals. The single-agent activity of high-dose methotrexate with rescue was first evaluated in breast cancer patients in a truncated Phase II study; 3 of 19 had a partial response (greater than 50% regression of measurable lesions) after 2 to 6 wk courses and another 6 to 19 had some objective evidence of response (greater than 25%, less than 50%). The response rate to the combination 'super-CMF' was: complete response (CR) 15 of 55 evaluable patients (27%) and partial response (PR) 28 of 55 (51%). The median duration of response was 24.5 mo and the median time to treatment failure was 21.6 mo. Nineteen of these patients have completed 12 to 18 mo of drug treatment and have been followed in continuing remission for 1 to 28 mo without further therapy. The total response rare and the CR rate achieved with this regimen are substantial, and the durability of the responses appears to be considerably greater than that obtained with other drug combinations. (Author abstract) (18 Refs)

23. STAGE III AND LOCALIZED STAGE IV BREAST CANCER: IRRADIATION ALONE VS IRRADIATION PLUS SURGERY.

Bedwinek J, Rao DV, Perez C, Lee J, Fineberg B
Div. Radiation Oncology, Mallinckrodt Inst. Radiology, Washington Univ., 4511 Forest Park, St. Louis, MO
Int J Radiat Oncol Biol Phys; 8(1):31-36 1982

One hundred and eighty-three patients with Stage III and localized Stage IV breast cancer were treated with radiotherapy alone (RT) or RT combined with surgery (RTS). Of the 147 patients with non-inflammatory carcinoma (NIC), 93 received RTS, and 54 RT. Of 36 patients with inflammatory carcinoma (IC), 29 were treated with RT, and the remaining 7 with RTS. In NIC patients, a significantly higher rate of local failure occurred in RT patients (61%) as compared with RTS (13%) patients. The regional failure rate was 37% in RT patients and 12% in RTS patients. The incidence of distant metastasis was the same for both groups, 65% vs 68%. The local failure rates were 45% for RT patients and 12% for RTS patients in the T3 NIC category, and 65% for RT patients and 13% for RTS patients in the T4 category. In both categories, the incidences of distant metastasis were essentially the same. Local failure rates were determined in relation to tumor size and treatment: 5-8 cm: 43% for RT, 14% for RTS; and 8 cm or greater: 76% for RT, 5% for RTS. There was no difference in the distant metastasis rates between the two treatment groups within the 5-8 cm and 8 cm or greater categories. The rate of local failure for the 29 patients with IC treated with RT was 52% compared to 14% for those treated with RTS. The difference in the regional failure rate between RT (38%) and RTS (29%) was determined. The rate of distant metastasis was essentially the same for the two treatment groups. With the exception of the six patients with tumors 0-5 cm, the incidence of local failure did not decrease with increasing total tumor dose. The most frequent complication, either moderate or severe, in the RT group was breast fibrosis (19%), while in the RTS group, arm edema (13%) was the most common complication. (20 Refs)

24. ADJUVANT COMBINATION CHEMOTHERAPY FOR OPERABLE BREAST CANCER. TRIALS IN PROGRESS AT THE ISTITUTO NAZIONALE TUMORI OF MILAN.

Bonadonna G, Rossi A, Tancini G, Bajetta E, Marchini S, Brambilla C, Tess JD, Valagussa P, Banfi A, Veronesi U
Istituto Nazionale Tumori of Milan, Via Venezian 1, 20133 Milan, Italy
Cancer Treat Rep; 65(Suppl1):61-65 1981

Adjuvant trials ongoing at the Istituto Nazionale Tumori of Milan for operable breast cancer with nodal involvement are reviewed in this paper. In the first trial (cyclophosphamide, methotrexate, 5-fluorouracil [CMF] vs control), the early 5-yr results confirm the usefulness of combination chemotherapy in significantly affecting the relapse-free survival (RFS) and total survival rates. The degree of axillary node involvement remains the most important prognostic indicator also in patients receiving adjuvant chemotherapy. The contention concerning the therapeutic effect of CMF in pre- vs postmenopausal women is overcome by the observation that about 80% of patients receiving greater than 85% of the planned dose are surviving relapse free at 5 yr regardless of their menopausal-status. The 3-yr results of the second CMF trial indicate that both RFS and total survival are comparable between the groups receiving 12 or 6 cycles of adjuvant CMF. The results were not affected by drug-induced amenorrhea nor by estrogen receptor status. Provided the percent of dose administered is high, there is probably no real advantage in prolonging CMF chemotherapy beyond the 6th mo. However, the results are still preliminary. (Author abstract) (17 Refs)

25. RESULTS IN PATIENTS WITH BREAST CANCER TREATED BY RADICAL MASTECTOMY AND POSTOPERATIVE IRRADIATION WITH NO ADJUVANT CHEMOTHERAPY.

Tapley ND, Spanos WJ, Fletcher GH, Montague ED, Schell S, Oswald MJ
(c/o Fletcher) Radiotherapy Dept., Univ. Texas, M.D. Anderson Hosp., 6723 Bertner Drive, Houston, TX, 77030
Cancer; 49(6):1316-1319 1982

In 1963 an electron beam became available, making irradiation of the chest wall technically easy. In addition to peripheral lymphatic irradiation in patients with positive axillary nodes and/or the tumor in the inner quadrants or centrally located, patients with tumor larger than 5 cm or with grave signs and/or a significant incidence of positive axillary nodes received chest wall irradiation. None of the patients has received elective chemotherapy. Disease-free survival rates at 10 yr are 54% for the overall group, 79% for the patients with negative nodes, 44% for patients with positive nodes, 61% for patients with 1-3 positive nodes, and 33% for patients with four or more positive nodes. The incidence of peripheral lymphatic failures is low as well as the incidence of failures on the chest wall in the patients having had chest wall irradiation. With the availability of electron beam and adjustments in doses, complications are nonexistent. The incidence of treatment failures, local-regional, or distant, that have appeared by 10 years are compared with the incidence of failures that were experienced by the placebo patients in the clinical trial of the NSABP of thio-TEPA versus placebo. The clearly lesser incidence of treatment failures in the University of Texas M D Anderson Hospital patients either suggests that postoperative irradiation may have survival benefits or that the data of the NSABP series are not representative of all series. (Author abstract) (17 Refs)

26. RADIOTHERAPY AS AN ADJUVANT IN THE TREATMENT OF CARCINOMA OF THE BREAST.

Nevin JE, Baggerly JT, Laird TK
990 Main St., Danville, VA, 24541
Cancer; 49(6):1194-1200 1982

During the period from 1950-1974, 510 patients with a diagnosis of invasive ductal carcinoma treated with the standard Halsted radical mastectomy were reviewed retrospectively from the records of the Tumor Clinic of The Memorial Hospital, Danville, Virginia. The primary aim of the study was to determine whether postoperative adjuvant radiation therapy (POART) as delivered in a community hospital setting contributed to better cancer control and effectively influenced 5 and 10 yr survival rates. The results of the review indicated that the use of POART whether from an orthovoltage or cobalt source did not differentially influence the patient's disease outcome. The use of POART did not improve the 5-and 10-yr survival rates regardless of lesion location in patients with Stages I, II, and III disease with positive lymph nodes. POART did cause a significant decline in 5-and 10-yr survival rates of patients with Stage II and III disease with negative nodes when compared to the survival of patients with the same stage of disease that did not receive POART, ie, 75% versus 94% 5-yr difference, and a 65% versus 85% 10-yr difference. These results suggest that radiotherapy may have a detrimental effect on immunocompetence and thus alter survival rates in certain circumstances. Therefore, any clinical investigation measuring the results of various therapeutic modalities singularly or in combination should be based on pathologic staging rather than clinical staging so that these factors can be adequately evaluated. (Author abstract) (41 Refs)

27. INFLAMMATORY BREAST CANCER TREATED WITH SURGERY, CHEMOTHERAPY AND ALLOGENEIC TUMOR CELL/BCG IMMUNOTHERAPY.

Wiseman C, Jessup JM, Smith TL, Hersh E, Bowen J, Blumenschein G

Immunotherapy Lab., St. Vincent Medical Center, 1231 West Third St., Los Angeles, CA, 90057

Cancer; 49(6):1266-1271 1982

Thirteen consecutive patients with inflammatory breast cancer were treated with a regimen consisting of cyclic chemotherapy, extended simple mastectomy, and immunotherapy utilizing irradiated allogeneic breast cancer cells admixed with BCG. When surgery was performed after two or more cycles of 5-Fluorouracil, doxorubicin hydrochloride, and cyclophosphamide, there was complete eradication of detectable tumor in 3 of 11 operative specimens. Two patients had surgery prior to our evaluation and four had prior chemotherapy. Chest wall radiation was initiated after 8-10 mo of chemotherapy at the doxorubicin cardiotoxicity limits. Seven untreated patients, all premenopausal, were compared to our previous series which employed either irradiation after several course of chemotherapy or irradiation alone. The current series has two relapses (8 mo, 25 mo) at a median follow-up time of 21 mo (range, 8-26 mo). In the previous chemoradiotherapy trial, all nine premenopausal patients had relapsed within 25 mo, with a median disease free interval of 17 mo. In the trial using radiotherapy alone, all 10 patients had relapsed by 19 mo (median disease free interval, 9 mo). The present regimen appears to improve control of the disease and further investigation of both surgery and immunotherapy intercalated with cyclic chemotherapy appears warranted in this disease. (Author abstract) (13 Refs)

28. ADJUVANT RADIATION THERAPY COMPARED WITH CYCLIC CHEMOTHERAPY IN PATIENTS WITH MAMMARY CARCINOMA. II. CHANGES OF MITOGEN RESPONSES OF BLOOD LYMPHOCYTES.

Strender LE, Blomgren H, Wasserman J, Petrini B, Baral E

Radiumhemmet, Karolinska Sjukhuset, S-104 01 Stockholm, Sweden

Acta Radiol Oncol Radiat Phys Biol; 20(5):299-304 1981

Blood lymphocyte reactivity to purified protein derivative of tuberculin (PPD) and phytohemagglutinin (PHA) was examined in 62 patients with breast carcinoma who received postoperative adjuvant radiation therapy or cyclic chemotherapy with chlorambucil, methotrexate and 5-fluorouracil. Both treatments impaired the immunologic reactivity of blood lymphocytes as measured by PPD and PHA stimulation in vitro. Radiation therapy seemed to cause more profound and protracted suppression of the PPD response than chemotherapy. (Author abstract) (20 Refs)

REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT

29. MYOCARDIAL ACCUMULATION OF 99MTC MDP IN PATIENTS SUBJECTED TO PROLONGED TREATMENT WITH ADRIAMYCIN. THE PROTECTIVE ACTION OF STROPHANTHIN AND VITAMIN E.

Ciambellotti E

Medicina Nucleare 'Rodolfo Caraccio', Ospedale degli Infermi, Biella, Italy

Minerva Med; 73(1/2):21-24 1982

Thirty-five patients (2 men, 33 women; 60.71 -16.8 yr old) with metastases (ME) due to mammary carcinoma were treated with adriamycin (40-60 mg/square meter, every mo), vincristine, and cyclophosphamide. K-Strophanthin (K-S: 0.125 mg) and vitamin E (VE: 210 mg) were administered 6 days before, during, and 6 days after the treatment with the anticancer agents. All of the patients were placed under cardiac control prior to each cycle of the treatment. Results of scintigraphy (SC) were evaluated according to Lyons. Myocardial and bone SC were performed after 550-650 MBq of 99mTc MDP was injected. The myocardial SC tests were performed in duplicate to avoid false positive results due to abnormal absorption by the thoracic wall. Tolerance of the antiblastic treatment was improved subjectively. Results of the SC indicated Grade 0 disease in 32 of the patients, Grade I in 2, Grade II in 3, and Grade III in none. Results of the SC performed on patients that did not receive the K-S and VE showed 18 patients with Grade 0 disease, 12 with Grade I, 2 with Grade II, and 3 with Grade III, as reported in an earlier study. The K-S and VE thus decreased the cardiac toxicity of the adriamycin. (27 Refs) (In ITA)

30. SUBCUTANEOUS MASTECTOMY: AN EVOLUTION OF CONCEPT AND TECHNIQUE.

Georgiade N, Serafin D, Georgiade G, McCarty KS

Div. Plastic and Reconstructive Surgery, Duke Univ. Medical Center, Dept.Surgery, Durham, NC, 27710

Ann Plast Surg; 8(1):8-19 1982

Indications for sc mastectomy are listed and the procedure is described. Patients in whom previous biopsies reveal extensive dysplastic changes with cytologic atypia in intraductal or intraacinar epithelial hyperplastic lesions are at high risk for malignancy. The patient's endocrinologic status should be evaluated. Vitamin E and danazol can be used in properly selected patients to reduce mastodynia and cystic disease. Patients must be informed of the various alternative therapies to sc mastectomy. Since as much as 10% of breast tissue may remain after sc mastectomy, the patient may still be at risk of malignancy. Sc mastectomy must be distinguished from other procedures in which the nipple areolar complex is removed and axillary node sampling is attempted. During sc mastectomy, only 1% of patients require nipple excision, carried out as a secondary procedure; routine nipple removal is needless in 99% of patients and may cause considerable additional psychological trauma. The procedure is described for patients with moderately hypertrophied and ptotic breasts, ptotic breasts, and massive hypertrophied ptotic breasts. Patients with carcinoma should undergo more extensive surgery with a modified or simple mastectomy. Nearly 20% of patients experience some undesirable capsule contracture. (Author abstract) (16 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

31. FECAL STEROID METABOLITES AND BREAST CANCER RISK.

Papatestas AE, Panvelliwalla D, Tartter PI, Miller S, Pertsemlidis D, Aufses AH

Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029

Cancer; 49(6):1201-1205 1982

Women with breast cancer (n = 78) had a higher excretion of total fecal steroids in mg/gm of dry weight (56 37) compared to controls (45 -29; n = 71) (p = 0.03). Increases in both total neutral steroids and total bile acids in cases contributed to this significant difference. Lean women (Quetelet's index less than 3.5) with breast cancer seemed to have inappropriately high excretion of total fecal steroids (56 -35), which was significantly higher than that of controls (41 -27) (p = 0.03). Obesity resulted in higher excretion of fecal steroids only in controls. The differences persisted, even after pairing control cases for race-ethnicity and menopausal status. In 59 such pairs, cases had higher values (56 -33), compared to controls (41 -26) (p = 0.008). Significant differences (p = 0.005) were also present in 24 post-menopausal pairs, while in 35 pre-menopausal pairs a similar trend, but no significant differences were noted. Women with benign breast disease had higher total fecal steroids (51 -34) compared to the other controls (38 -21) (p = 0.05). This observation suggests a common etiology between benign breast disease and breast cancer. There were no significant differences in dietary intake of total calories, total fat or dietary cholesterol between controls and cases suggesting that the observed differences in fecal steroids could be attributed to higher endogenous synthesis of cholesterol in cases. (Author abstract) (23 Refs)

32. BREAST CANCER IN WOMEN AGED 30 AND UNDER.

Noyes RD, Spanos WJ, Montague ED

(c/o Spanos) Section Radiation Oncology, Loma Linda Univ. Medical Center, Loma Linda, CA, 92354

Cancer; 49(6):1302-1307 1982

Breast cancer in women 30 years of age or less accounts for 2% of all breast cancers seen today. At M D Anderson Hospital, 310 young women in this age group were seen, 141 of whom received their primary treatment there. After excluding all those with inflammatory and noninvasive carcinomas, 125 patients were analyzed for survival according to nodal status, lesion size, and pregnancy status. This group was compared to a similarly matched group of 3,380 women over age 30 yr also treated at this institution. Young women with negative nodes and those with lesions less than 5 cm in size were found to have significantly poorer survivals than older women in the same groups, in contrast to several recent reports on this subject. (Author abstract) (22 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

33. LECTIN AGGLUTINABILITY OF MAMMARY TUMOURS WITH DIFFERING METASTATIC COLONISATION POTENTIALS.

Price JE, Tarin D
(c/o Tarin) Dept. Histopathology, Univ. Oxford, John Radcliffe Hosp., Headington, Oxford, OX3 9DU, England
Differentiation; 20(3):264-269 1981

A new fully quantitative method for assessment of lectin agglutinability has been used in this investigation to compare the surface composition of cells from tumors with high and low pulmonary colonization potential. As in our previous work, we have used only primary (ie, naturally-occurring) mammary tumors in mice. It was found that agglutinability with the lectins Concanavalin-A and Wheatgerm agglutinin bore no relationship to the pulmonary colonizaiton potential of the primary mammary tumor. However, cells from disaggregated secondary deposits of tumors which manifested high colonization potential were consistently less agglutinable than the cells of the primary tumors from which they were derived. (Author abstract) (16 Refs)

34. HORMONAL REGULATION OF HUMAN BREAST CANCER CELLS IN VITRO.

Lippman M, Meites J, Welsch CW, Rosen JM, Segaloff A, Korenman SG, Nandi S, Sirbasku DA
Medical Breast Cancer Section, Medicine Branch, NCI, Bethesda, MD, 20205
Banbury Rep; 8:171-184 1981

Cultured breast cancer cell lines (most of which were derived from neoplastic effusions, often after treatment) differ from the original tumors in several important ways. Experiments with these cell lines must be designed and their results interpreted with great caution. Firm conclusions as to the absence of a given hormone response are particularly difficult to interpret. Positive results are much less ambiguous, but these can also give rise to misinterpretations. Nevertheless, the cell-culture approach provides several advantages in the investigation of hormonal interactions with human breast cancer. In particular, drug- and hormone-resistant variants of wild-type parental cell lines can be used to study the mechanisms of hormone dependence. Hormones now known to affect the growth or differentiated functions of human breast cancer cells (especially the MCF-7 cell line) include estrogens, glucocorticoids, androgens, thyroid hormones (the ZR-75-1 cell line is absolutely dependent on physiologic levels of triiodothyronine in the medium, and MCF-7 cells are also thyroid hormone dependent), and insulin. Vitamin A derivatives are required for normal epithelial differentiated and inhibit several types of chemical carcinogenesis in rats. Several human breast cancer cell lines contain separable binding activities for retinol and retinoic acid, but clinical trials of 13-cis-retinoic acid in breast cancer patients have not been encouraging. The roles of epidermal growth factor, vitamin D, progesterone, and prolactin in breast cancer growth are not yet clear. (46 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Aufses AH 31
Baggerly JT 26
Bajetta E 24
Baldauf K 8
Banfi A 24
Baral E 28
Barnes JM 4
Battersby C 2
Bear B 3
Bedwinek J 23
Blamey RW 11
Blomgren H 28
Blumenschein G 27
Bonadonna G 24
Botta G 18
Bowen J 27
Brambilla C 24
Bussolati G 18
Campbell FC 11
Canellos GP 22
Ciambellotti E 29
Contesso G 10
Cowan K 12
Cox EB 17
De Carli HO 15
Delarue JC 10
Dilley WG 17
Dinsdale EA 19
Dinsdale EA 20
Edwards PA 19
Edwards PA 20
Egan RL 21
Elston CW 11
Fineberg B 23
Fletcher GH 25
Foster CS 19
Foster CS 20
Francesconi M 7
Frei E 22
Fritze D 16
Fulk CH 1
Garratt KN 14
Gelman R 22
George D 11
Georgiade G 30
Georgiade N 30
Gilchrist KW 4
Gilson AJ 3
Giorlando S 14
Goldstein DP 9
Gould VE 4
Griffiths K 11
Gugliotta P 18
Haagensen DE 17
Hartveit F 5
Hase T 6
Henderson IC 22
Hernandez AM 14
Hersh E 27
Hirschl S 4
Horwitz KB 13
Ibsen KH 14
Imbriglia JE 4
Jakesz J 7
Jessup JM 27
Kaufmann M 16
Korenman SG 34
Laird TK 26
Lee J 23
Leight GS 17
Lippman M 12
Lippman M 34
Mansour EG 4
Marchini S 24
Maturo VG 3
May-Levin F 10
McCarty KS 30
McLendon MS 1
Meites J 34
Miler V 9
Miller S 31
Montague ED 25
Montague ED 32
Morz R 7
Moser K 7
Mouriesse H 10
Nandi S 34
Neville AM 19
Neville AM 20
Nevin JE 26
Nicholson RI 11
Noyes RD 32
Nungaray G 14
Orlando RA 14
Oswald MJ 25
Panvelliwalla D 31
Papatestas AE 31
Patchefsky AS 4
Penner DW 4
Perez C 23
Pertsemlidis D 31
Petrini B 28
Pickren J 4
Price JE 33
Rainer H 7
Rao DV 23
Restberg V 15
Rosen JM 34
Rossi A 24
Sancho-Garnier 10
Sato Y 6
Schell S 25
Schemper M 7
Schicke B 8
Schwartz IS 4
Segaloff A 34
Serafin D 30
Silva JS 17
Sirbasku DA 34
Smith TL 27
Spanos WJ 25
Spanos WJ 32
Starnes DC 1
Strender LE 28
Suzuki M 6
Takeda T 6
Tallos PB 17
Tancini G 24
Tangen M 5
Tapley ND 25
Tarin D 33
Tartter PI 31
Tess JD 24
Thoresen S 5
Valagussa P 24
Veronesi U 24
Wasserman J 28
Wells SA 17
Welsch CW 34
Wheeler JE 4
Wiseman C 27
Zur Horst-Meyer 8
Zusmer NR 3

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In this issue:

- **DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS** 1-5
- **BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS** 6-9
- **CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS** 10
- **BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)** 11-22
- **SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)** 23-25
- **SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY** 26-29
- **SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)** 30-31

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DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

1. NUCLEAR MAGNETIC RESONANCE IMAGING AND EVALUATION OF HUMAN BREAST TISSUE: PRELIMINARY CLINICAL TRIALS.

Ross RJ, Thompson JS, Kim K, Bailey RA
Suite 206, Hillcrest Medical Building I, 6803 Mayfield Road, Mayfield Heights, OH, 44124
Radiology; 143(1):195-205 1982

In vivo clinical evaluations of human mammary tissue, including normal, dysplastic, and neoplastic breasts, were initiated using the FONAR method of nuclear magnetic resonance (NMR) imaging. Spin-lattice relaxation times (T1) were determined and correlated with other diagnostic modalities including mammography, xeroradiography, and sonography. Normal breasts and breasts with extensive fatty replacement were found to have the lowest T1 values, whereas T1 values of malignant tissue were elevated. T1 values for mammary dysplasia extended over a wide range, and NMR images exhibited lower proton density than normal tissue. In several patients with severely dysplastic breasts, T1 values overlapped those from patients with documented breast neoplasms. Markedly elevated T1 values were obtained from fluid-filled cysts that were well beyond the range of malignancy. (Author abstract) (17 Refs)

2. VALUE OF PRE-TREATMENT AND FOLLOW-UP SKELETAL SCINTIGRAPHY IN OPERABLE BREAST CANCER.

Pauwels EK, Heslinga JM, Zwaveling A
Dept. Diagnostic Radiology, Div. Nuclear Medicine, Univ. Hosp., Leiden, The Netherlands
Clin Oncol; 8(1):25-32 1982

Bone scintigraphy has been performed between 1973 and 1977 for preoperative detection of osseous metastases in patients with operable mammary malignancy. In 81 patients, classified as Columbia A no malignant bone lesions were detected. In 55 patients, mainly classified as Columbia B and some as Columbia C, altogether four cases with bone metastases have been found. Thus, bone scintigraphy was informative in only 4 out of 136 cases (2.9%). These four cases suffered from bone pain and/or had elevated alkaline phosphatase levels. Follow up of our group of patients over a period of 4 yr has shown that bone metastases predominantly occur in the first 2 postoperative yr. In seven patients, classified as Columbia A and in eight patients classified as Columbia B/C bone metastases were scintigraphically detected in these first 2 yr. Also in these patients bone pain and/or an elevated alkaline phosphatase level was present. It would have required approx 520 serial bone scans, each with 1/2 yr interval, to detect these 15 cases. Cost benefit evaluation has shown that both pre-operative and postoperative bone scintigraphy in patients with operable breast carcinoma is not indicated. We believe that boner pain and/or biochemical changes may serve as an indication for bone scanning in this group of patients. (Author abstract) (28 Refs)

3. BIAS AND THE ASSOCIATION OF MAMMOGRAPHIC PARENCHYMAL PATTERNS WITH BREAST CANCER.

Boyd NF, O'Sullivan B, Campbell JE, Fishell E, Simor I, Cooke G, Germanson T
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada
Br J Cancer; 45(2):179-184 1982

We have carried out a case-control study to evaluate the association between Wolfe's mammographic patterns and the risk of breast cancer, and to examine the influence of control selection and the radiologist who reads the films upon the results obtained. Mammograms of the non-cancerous breast of 183 women with unilateral breast cancer were compared with mammograms from two age-matched control groups: a group of asymptomatic women attending a screening center, and a group of symptomatic women referred for the diagnostic evaluation of suspected breast disease. Films were arranged in random sequence and independently classified by three radiologists. A strong and statistically significant association was found between mammographic dysplasia and breast cancer when controls from the screening center were compared to cases, but not when cases were compared to women referred for the diagnostic evaluation of breast disease. This result appears to arise in part because of an association between symptoms of benign breast disease and mammographic dysplasia, and suggests that some previous negative studies of the association of mammographic patterns with breast cancer may have arisen from the inclusion of symptomatic subjects as controls. (Author abstract) (23 Refs)

4. MAMMOGRAPHIC SIGNS AS RISK FACTORS FOR BREAST CANCER.

Boyd NF, O'Sullivan B, Campbell JE, Fishell E, Simor I, Cooke G, Germanson T
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada
Br J Cancer; 45(2):185-193 1982

We have carried out a case-control study to examine the relationship between mammographic signs and breast cancer. The mammographic signs assessed were prominent ducts and dysplasia. The cases were a group of 183 women with histologically verified unilateral breast cancer. The controls were a group of women attending a screening center. Cases and controls were individually age-matched. Mammograms from the non-cancerous breast of the cases were randomly assembled with those of the controls and classified by three radiologists without knowledge of which films were from cases and which from controls. Mammographic dysplasia was found to be strongly associated with breast cancer, particularly in women aged less than 50. Prominent ducts were only weakly associated with breast cancer. Multivariate analysis showed that the association between dysplasia and breast cancer could not be explained on the basis of other risk factors for breast cancer, and that classification of dysplasia discriminated more strongly between cases and controls than did classification of Wolfe's mammographic patterns. These results show that mammograms contain information about risk of breast cancer. Mammographic dysplasia is strongly associated with breast cancer, is present in a substantial proportion of patients with the disease, and may offer opportunities for prevention. (Author abstract) (27 Refs)

5. THE VALUE AND FEASIBILITY OF PUNCTURE CYTOLOGY IN THE DIAGNOSIS OF SOLID TUMORS OF THE BREAST. A STUDY OF 1,292 NEW CASES.

Verhaeghe M, Cornillot M, Laurent J, Verhaeghe J
Technique Chirurgicale, Faculte de Medicine, 1, place de Verdun, 59045 Lille, France
Chirurgie; 107(8):652-655 1981

The results of puncture cytology biopsy of 1,292 solid breast tumors are reported. Malignant tumors (901; 871 invasive) were more common than benign tumors (391). Clinical diagnoses made 96 errors with 72 false negatives and 24 false positives results. Cytology was responsible for 74 errors with 61 false negatives (6.7%) and 13 false positives (3.3%) results . Of the 96 clinical errors, 72 were corrected by cytology. Of the 73 cytologic errors, 50 were correct with clinical diagnosis. There were 24 errors which both methods made in common. Results were improved with the use of mammography. When all three methods were used, only 12 cancers were undiagnosed and there was one false diagnosis. The total number of errors (13) corresponds to 1% error which is similar to other series using the three diagnostic techniques. Based on the above results, the systemic use of cytology and mammography is recommended in order to obtain a triple diagnosis which provides the certitude when all results agree and which provides a dependable alert system when results are contradictory. (no Refs) (In FRE)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

6. IMMUNOHISTOCHEMICAL LOCALIZATION OF ESTROGEN RECEPTORS IN HUMAN MAMMARY CARCINOMA USING ANTIBODIES TO THE RECEPTOR PROTEIN.

Raam S, Nemeth E, Tamura H, O'Briain DS, Cohen JL
Oncology Lab., Tufts Univ. Medical Cancer Unit, Lemuel Shattuck Hosp., 170 Morton St., Boston, MA, 02130
Eur J Cancer Clin Oncol; 18(1):1-12 1982

An immunofluorescent method has been developed for localizing estrogen receptors (ER) in frozen sections of human breast cancer biopsies which utilizes the biochemically well-characterized antibodies to the cytoplasmic ER of human breast cancer produced in rabbits. Frozen sections of 16 breast cancer biopsies, in which the receptor content has been quantified using dextran-coated charcoal assay (DCC technique), were used to study the localization of ER. Two aspects of ER detection, namely 'estrogen-binding' and ability to react with the homologous antibodies, have been analyzed and the results compared with those of DCC technique. Fluorescent labeled estrogen method (F-E2) of Pertschuk was utilized to detect the distribution of estrogen binding proteins and the indirect immunofluorescent (IM-AR) method using antireceptor antibodies to assess the antigenic sites of the receptor protein. In addition to the comparison of the results of three techniques, DCC, IM-AR and F-E2, for ER detection, a procedure for processing the frozen sections, which enables the study of estrogen binding characteristic as well as the antigenic reactivity of the receptor molecules, is described. (Author abstract) (10 Refs)

7. CELLULAR LOCALIZATION OF ESTROGEN BINDING SITES IN HUMAN BREAST CANCER.

Hanna W, Ryder DE, Mobbs BG
Dept. Lab., Women's Coll. Hosp., 76 Greenville St., Toronto, Ontario M5S 1B2, Canada
Am J Clin Pathol; 77(4):391-395 1982

Biopsy specimens from 52 consecutive cases of primary human breast cancer were collected over a period of 7 mo and included in a study for histochemical localization of estrogen binding sites (EBS), using a fluorescein labeled Estradiol conjugate. Cryostat frozen sections from each tumor were examined to determine the localization of the tracer and to evaluate the percentage of positive cells in a given tumor. Results are correlated with the values of the biochemical assay for the estrogen receptor (ER) protein done on the same tumor. The localization of EBS by a tracer is a simple technique that can be done and interpreted in any surgical pathology laboratory. It was concluded that this method could be a valuable supplementary technique to the biochemical assay; allowing more accurate selection of patients and prediction of their response to endocrine therapy. Clinical follow-ups are extremely necessary to evaluate the suitability and the accuracy of the technique in choosing breast cancer patients for endocrine manipulation. (Author abstract) (17 Refs)

8. ASSAY OF ESTRADIOL RECEPTORS IN HUMAN BREAST CARCINOMAS USING THE GAMMA EMITTING LIGAND 16ALPHA[125I]IODOESTRADIOL.

Duffy MJ
Dept. Nuclear Medicine, St. Vincent's Hosp., Dublin 4, Ireland
J Steroid Biochem; 16(2):343-344 1982

The use of 16alpha[125I]iodoestradiol to assay estrogen receptor (ER) in human breast carcinoma was investigated. A constant amount of cytosol was incubated at five different concentrations of radiolabeled estradiol overnight at 4 C, and non-specific binding was measured with parallel incubations in the presence of 100-fold excess unlabeled diethylstilbestrol (DES). Excess unlabeled estradiol and DES were the most potent inhibitors of binding, estrone and estriol were less potent, and testosterone, progesterone, and cortisol were ineffective. The affinity of iodoestradiol for breast tumor ER was similar to that of tritiated estradiol in 19 carcinoma cytosols. Good agreement was found between results using tritiated and iodoestradiol as ligands (correlation coefficient = 0.97). Twelve tumors contained less than 50 femtomoles ER by both ligands. Good agreement was observed between the use of a single saturating concentration of 5 nanoM iodoestradiol and the Scatchard plot analysis using the same ligand (correlation coefficient = 0.97). Advantages of using a gamma-emitting ligand for the assay of ER in breast tumor tissue are listed. (4 Refs)

9. ASSOCIATION OF PLASMINOGEN ACTIVATOR ACTIVITY AND STEROID RECEPTORS IN HUMAN BREAST CANCER.

Thorsen T
Hormone Lab., Univ. Bergen Sch. Medicine, Bergen, Norway
Eur J Cancer Clin Oncol; 18(2):129-132 1982

Plasminogen activating activity (PAA) has been determined in 105 human breast cancer cytosols with a colorimetric assay. PAA has been related to steroid receptors in the same cytosols. A strong positive correlation between PAA and progesterone receptor levels was found (Spearmans coefficient of rank correlation, R_s = 0.74, p less than 0.001). PAA discriminates between progesterone receptor-positive and -negative tumors, irrespective of estradiol receptor content. It is suggested that PAA is a marker of functional estradiol receptor and that fibrinolytic activity may be a causative factor in the low metastatic potential of progesterone receptor-positive tumors. (Author abstract) (25 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

10. A SIMULTANEOUS STUDY OF FIVE MARKERS IN 80 CASES OF BREAST CANCER. CARCINO-EMBRYONIC ANTIGEN (CEA), FERRITIN BETA2, MICROGLOBULIN, (BETA M), SUB-UNIT BETA OF CHORIONIC GONADOTROPHIN HORMONE (BETA CGH) AND ALPHA FETOPROTEIN (AFP).

Fourrier Y, Kadouche J, Mignot L, Reynier J, Gorins A, Rochet Y, Trevoux R, Gavel M
Centre des Maladies du Sein, Hopital Saint-Louis, 38, rue Bichat, F 75010 Paris, France

Gynecologie; 32(4/5):385-390 1981

Pathological levels of CEA, ferritin (FT), microglobulin (beta M), (CGH), and alpha fetoprotein (AFP) were compared in various stages of breast cancer (80 cases). When the pathologic level of CEA was set at 2.5 nanograms (nanog)/ml, there were positive results in 63% of the cases at diagnosis, 95% of the metastasized cancers, and 42% of the postoperative cases. When the pathologic level of CEA was set at 4 nanog/ml, the percentages of positive cases were 35%, 91%, and 35% respectively. In all cases, the highest positive values were obtained with CEA and FT. The value of beta M was more limited, and CGH and AFP provided very little information. In 18 metastasized cases which were treated with chemotherapy, CEA assays evolved along parallel lines with the clinical course of the disease in 16 cases and in 2 cases, levels of CEA increased while the disease seemed stable. FT evolved along clinical lines in 17 cases, but levels increased in 1 case which seemed to be in regression. The other assay results did not correlate in any significant way with clinical course of the disease. Based on the results of this study, it is recommended that CEA and FT be used to monitor the progress of patients who have been surgically treated for breast cancer and are undergoing adjvant therapy. (15 Refs) (In FRE)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

11. PEPTICHEMIO VERSUS MELPHALAN (L-PAM) IN ADVANCED BREAST CANCER.

Buzdar AU, Legha SS, Blumenschein GR, Hortobagyi GN, Yap HY, Schell FC, Barnes BC, Fraschini G, Bodey GP
Medical Breast Service, Dept. Medicine, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030

Cancer; 49(9):1767-1770 1982

Peptichemio is a polypeptide complex of L-phenylalanine mustard. Because of structural similarities between melphalan (L-PAM) and Peptichemio, a prospective randomized study was done to compare the therapeutic efficacy of these two agents. After failing various combinations of doxorubicin, cyclophosphamide, fluorouracil, methotrexate, and vincristine patients with advanced breast cancer were randomized to receive either Peptichemio or L-PAM. Peptichemio was administered at 75-100 mg/m2 and L-PAM at 30-40 mg/m2 iv q 3-4 wk interval. Of 56 evaluable patients, 28 received peptichemio and 28 received L-PAM. There were no objective responses in the L-PAM group, and disease stabilized in four patients (14%). The median duration of stable disease was 3 mo (range, 3-4 mo). In the peptichemio group seven patients (25%) achieved a partial remission, one patient (3%) achieved less than partial remission and three patients (11%) had stable disease. The median duration of response was 6 mo (range, 5-7+ mo) for responding patients and 3 mo (range, 2-5 mo) for stable disease. The major toxicity of both drugs was myelosuppression which was cumulative. In conclusion, peptichemio is an active agent in advanced breast cancer, but L-PAM is ineffective in previously treated patients with metastatic breast cancer. (Author abstract) (9 Refs)

12. N-(PHOSPHONACETYL)-L-ASPARTATE (PALA) IN ADVANCED BREAST CANCER: A PHASE II TRIAL OF THE EORTC BREAST CANCER COOPERATIVE GROUP.

Paridaens R, Mouridsen HT, Palshof T, Cocconi G, Van Oosterom A, Rotmensz N, Sylvester R, Heuson JC, Rozencweig M

Service de Medecine et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut Jules Bordet, 1, rue Heger-Bordet, 1000 Bruxelles, Belgium

Eur J Cancer Clin Oncol; 18(1):67-70 1982

Twenty-nine evaluable patients with extensively pretreated breast cancer received PALA, a new pyrimidine antimetabolite. The drug was given by intravenous infusion over 60 min, at a daily dose of 2.5 g/m2 for 2 consecutive days. Courses were repeated a 2-wk intervals and doses were escalated to toxicity. Two objective partial remissions were observed, lasting for 3 and 4.5 mo respectively. Toxic effects were dose-related and consisted mainly of mucocutaneous manifestations, ie, skin rashes, stomatitis, diarrhea, conjunctivitis and corneal ulcerations. Evidence of antitumor potential in far-advanced disease and lack of myelosuppression point to the need for additional trials of PALA in a more favorable selection of patients with breast cancer. (Author abstract) (21 Refs)

13. ADJUVANT TAMOXIFEN THERAPY FOR EARLY BREAST CANCER: AN EXPERIMENTAL STUDY WITH REFERENCE TO OESTROGEN AND PROGESTERONE RECEPTORS.

Wilson AJ, Tehrani F, Baum M

Dept. Surgery, King's Coll. Hosp. Medical Sch., Denmark Hill, London SE5 8RX, England

Br J Surg; 69(3):121-125 1982

There is very little known about the subsequent behavior of breast cancer following adjuvant endocrine therapy or the effect of this therapy on the estrogen and progesterone receptor content of recurrent disease. Mammary tumors were induced in Sprague-Dawley rats using N-nitrosomethylurea. In two experiments animals were treated with tamoxifen at different doses prior to the appearance of tumors. Tamoxifen prolonged the induction time and reduced the total number of tumors. Subsequent treatment of established tumors exposed to tamoxifen in the induction period demonstrated a reduced response to further tamoxifen therapy. There was no difference in the estrogen receptor content of the tumors previously exposed to tamoxifen, but there was a significant reduction in the progesterone receptor content. The results suggest that: (a) patients treated with adjuvant tamoxifen therapy will show a delay in the appearance of recurrent disease with a reduced response to further tamoxifen therapy; (b) the model may provide an in vivo method to examine the relationships between estrogen and progesterone receptors and response to endocrine therapy. (Author abstract) (34 Refs)

14. OPTIMAL SCHEDULING OF METHOTREXATE AND 5-FLUOROURACIL IN HUMAN BREAST CANCER.

Benz C, Tillis T, Tattelman E, Cadman E
(c/o Cadman) Dept. Medicine and Pharmacology, Yale Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(5):2081-2086 1982

We have shown previously that methotrexate pretreatment of murine leukemia and human colon carcinoma cell cultures results in augmented intracellular accumulation of 5-fluorouracil metabolites. Both of these drugs are commonly used for the treatment of women with breast cancer; thus, sequencing of methotrexate before 5-fluorouracil was evaluated in vitro using a human mammary carcinoma cell line, 47-DN. Intracellular 5-fluorouracil accumulation was maximally increased 4-fold in cultures pretreated with 10 uM methotrexate for 24 hr. This enhancement of 5-fluorouracil metabolism was associated with increased intracellular levels of 5-phosphoribosyl 1-pyrophosphate, resulting from the antipurine effect of methotrexate. Brief exposure to exogenous hypoxanthine at physiological concentrations reversed the biochemical synergism between methotrexate and 5-fluorouracil. Other antimetabolites associated with elevations of 5-phosphoribosyl 1-pyrophosphate enhanced intracellular accumulation of 5-fluorouracil up to 2.5-fold. In cloning assays, 18 hr of methotrexate pretreatment followed by 5-fluorouracil resulted in optimal synergistic cytotoxicity, which could be prevented if high concentrations of leucovorin were given between methotrexate and 5-fluorouracil administration. Since these results indicated that optimal breast tumor toxicity in vitro was achieved by 18-to 24-hr sequencing of methotrexate and 5-fluorouracil, a clinical toxicity study was carried out to assess whether this drug schedule could be tolerated. Seven patients with advanced cancer were treated with 21 courses of sequential therapy. No toxicity occurred with 38% of treatment courses; mild to moderate leukopenia and mucositis occurred with 29 and 38% of courses, respectively. Toxicity was related to retreatment interval and not cumulative drug dose or elevated serum methotrexate levels. These clinical results suggest that Phase II studies evaluating 24-hr-sequenced methotrexate and 5-fluorouracil in breast cancer are warranted. (Author abstract) (31 Refs)

15. TAMOXIFEN AS INITIAL SOLE TREATMENT OF LOCALIZED BREAST CANCER IN ELDERLY WOMEN: A PILOT STUDY.

Preece PE, Wood RA, Mackie CR, Cuschieri A
Univ. Dept. Surgery, Ninewells Hosp. and Medical Sch., Dundee DD1 9SY, Scotland
Br Med J; 284(6319):869-870 1982

In a 4-yr pilot study, 67 women (75 yr old or more) with apparently localized breast cancer were treated with tamoxifen (10-20 mg bid) in view of its proved efficacy in advanced breast cancer in this age group. Forty-nine patients (73%) responded sufficiently to persist with treatment beyond the first follow-up visits. Response rates for Stage II and III tumors were similar; however, the time to become impalpable was longer for the larger lesion. Nine patients (18%) required greater than 12 mo to achieve satisfactory response. The drug was well tolerated in all patients. In 9/18 patients in whom tamoxifen failed at the outset, tumor size was static, while tumor size increased in 9 (gradually in 3). Three relapses occurred in the tamoxifen treatment group; one case after a 12-mo remission, and two cases of partial remission followed by local disease progression. Of the group in which tamoxifen failed, 12 underwent mastectomy. While results of tamoxifen use seem encouraging as a way to spare this age group the stress of surgery and hospital admission, comparison with mastectomy and tylectomy in a clinical trial is needed. (5 Refs)

16. EVALUATION OF FOLLOW-UP METHODS TO DETECT RELAPSE AFTER MASTECTOMY IN BREAST CANCER PATIENTS.

Cantwell B, Fennelly JJ, Jones M
Dept. Medical Oncology, St. Vincent's Hosp., Elm Park, Dublin 4, Ireland
Ir J Med Sci; 151(1):1-5 1982

Out of 84 patients studied, 42 had recurrence of breast cancer, 1 patient developed a second primary carcinoma, and 41 patients remained disease free. The most useful means of first detection of recurrence was patient symptomatology: bone pain was most frequently reported and occurred in 24 (57.1%) who relapsed. Physical examination gave first evidence of relapse in 12 patients (28.5%). Frequent serial measurements were made of carcinoembryonic antigen, alkaline phosphatase and erythrocyte sedimentation rate; values were more commonly abnormal in patients with relapse. Although these tests are not entirely reliable, they are inexpensive, easy to perform, and may identify early distant metastases. Isotope bone scans and chest x-rays detected relapse reliably only in those patients with clinical abnormalities or abnormal blood tests. (16 Refs)

17. SEQUENTIAL HORMONE-CHEMOTHERAPY (MAP AT HIGH DOSES AND CMF) IN METASTATIC BREAST CANCER. PRELIMINARY RESULTS.

Pannuti F, Di Marco AR, Rossi AP, Rocchetta G, Rubino I, Giovannini M, Fruet F
Osp. M. Malpighi, Via Albertoni, 15, 40138 Bologna, Italy
Panminerva Med; 23(2):93-96 1981

The results we report refer to 22 patients with advanced breast cancer, who underwent sequential hormone-chemotherapy (Medroxyprogesterone acetate, MAP, at high doses and cyclophosphamide, fluorouracil and methotrexate (CMF)). As to the treatment with MAP, 7 patients received a dose of 500 mg/day/im for 30 days, 12 a dose of 1,500 mg/day/im for 30 days and 3 a dose of 2,000 mg/day/im for 30 days. We obtained a 59% (13/22) objective response with MAP and 41% (9/22) with CMF. The overall number of responders to at least one treatment was 17/22 (77%), while 4/22 didn't respond to either treatment. The analysis of the actuarial curve of survival shows significant differences between the patients who responded to both treatments and those who didn't respond to either. The authors conclude by stating that, on the ground of the data available at the moment, sequential hormone-chemotherapy seems to give not worse results than the combination therapy. In addition, a prior therapy with MAP doesn't alter the response to the following chemotherapy. However to decide which therapy type, combined or sequential, is better, we need a larger casuistics and prospective and randomized studies. (Author abstract) (18 Refs)

18. EFFECTS OF ENDOCRINE THERAPY ON STEROID-RECEPTOR CONTENT OF BREAST CANCER.

Taylor RE, Powles TJ, Humphreys J, Bettelheim R, Dowsett M, Casey AJ, Neville AM, Coombes RC
(c/o Coombes) Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 45(1):80-85 1982

In order to determine the mechanisms of relapse following response to endocrine therapy, we have measured the estrogen receptor (RE) content of biopsies of breast cancer in patients receiving various types of endocrine treatment. RE content fell in responding (means of 260.2 to 12 fmol/mg protein) and in nonresponding (means of 155.1 to 31.8 fmol/mg protein) patients who had measurable receptor at the start of treatment. Some of these patients, and a further group of responders to endocrine therapy, were monitored until relapse. Tumor biopsies at the time of relapse showed that 10/14 tumor samples contained significant RE (mean of 86.7 fmol/mg protein; range less than 10-271 fmol/mg protein) after successful endocrine therapy. No relationship could be found between RE content and plasma gonadotrophin or steroid-hormone concentration, but the fall in RE content correlated with reduced numbers of tumor cells in the biopsy. These results indicate that relapse following successful endocrine therapy in breast cancer does not appear to be due to the emergence of RE-negative tumor cells. The fall in RE content during response to endocrine therapy may be due to reduced tumor-cell content of the biopsy. (Author abstract) (19 Refs)

19. ADRIAMYCIN THERAPY BY CONTINUOUS INTRAVENOUS INFUSION IN PATIENTS WITH METASTATIC BREAST CANCER.

Legha SS, Benjamin RS, Mackay B, Yap HY, Wallace S, Ewer M, Blumenschein GR, Freireich EJ
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9):1762-1766 1982

Patients with metastatic breast cancer previously treated with non-Adriamycin containing chemotherapy were treated with Adriamycin at a dose of 60 mg/m2 administered as a continuous infusion through a central venous catheter. The duration of adriamycin infusion was escalated by 100% increments from 24-96 hr, but the majority of patients were maintained on 96-hr infusions. Thirteen of 27 patients achieved objective response (1 CR, 12 PR), 6 improved, and 8 failed to respond to adriamycin. Administration of adriamycin by infusion led to a decrease in the severity of nausea and vomiting, but had no effect on myelosuppression and alopecia secondary to adriamycin. The cardiac toxicity of adriamycin was reduced in patients who received maintenance therapy with 96-hr infusions of adriamycin. (Author abstract) (14 Refs)

20. THE PLACE OF RADIOTHERAPY AS A PRIMARY MANAGEMENT OF BREAST CANCER.

Nervi C, Arcangeli G, Danesi DT, Creton G
Istituto Medico e di Ricerca Scientifica, Via Luigi Bodio 58, 00191 Rome, Italy
Tumori; 68(1):73-80 1982

From March 1972 to November 1979 a total of 157 patients with Stage I to III primary breast cancers have been irradiated after segmental resection (12 cases), tylectomy (89 cases) or biopsy (56 cases). Complete local control was achieved in all Stage I lesions, in 97% Stage II lesions and in 68% Stage III lesions. Nonrecurrence has been observed in patients previously operated by segmental resections, while local failures occurred in 6/89 and in 16/56 patients operated by tylectomy or biopsy, respectively. Of the 28 Stage I patients, 24 (86%) are alive, 1 with distant metastases. Four patients of this group are dead, two of intercurrent disease and two of breast cancer. Of the 61 (Stage II) patients, 38 (62%) are alive, 5 of these with distant metastases. Twenty-three patients are dead, 15 with active disease, and 8 suffered intercurrent death. Of the 68 Stage III patients, 21 (31%) are alive, 6 of these with distant metastases. Forty-seven patients are dead, 43 of breast cancer and 4 of intercurrent disease. The high probability of initial subclinical deposits is evidenced by the fact that 49 of the 68 patients in this group developed distant metastases. The patients with T1 lesions appear to comprise the most favorable group with a relapse free survival at 5 yr of 76%. The 5-yr relapse free survival was 62% for T2 lesions and 25% for T3 and T4 lesions. N0 status does not confer the same favorable prognosis as T1 status. N+ status, however, resulted in a definitely negative prognostic factor. Cosmetic results after our treatment approach appear to be extremely good. A marked difference between the irradiated and contralateral breast occurred only in 10 of the 125 patients after a minimum of 2 yr' observation. (Author abstract) (27 Refs) (In ITA)

21. INITIAL CHEMOIMMUNOTHERAPY IN INFLAMMATORY CARCINOMA OF THE BREAST.

Zylberberg B, Salat-Baroux J, Ravina JH, Dormont D, Amiel JP, Diebold P, Izrael V
Dept. Chemotherapy, Hopitaux Bichat and Tenon, 36 Ave. Simon Bolivar, 75019 Paris, France
Cancer; 49(8):1537-1543 1982

Fifteen patients with clinical primary inflammatory carcinoma of the breast were treated with initial chemoimmunotherapy between September 1974 and 1977. The protocol was a combination of Adriamycin, vincristine, 5-fluorouracil, and methotrexate given by iv push, and melphalan per os. Thermographic cooling was taken as the criterion of operability. Initial chemotherapy was resumed after surgery up to a total of 10 courses and followed by maintenance chemotherapy for a min of 1 yr. Immunotherapy using I-BCG-F Pasteur was routinely associated with the antimitotic agents. The median survival for our 15 patients has not been reached and exceeds 56 mo. These results correspond to an obvious therapeutic benefit compared with recent attempts in which similar chemoimmunotherapy protocols were used; this benefit seems to be the consequence of the adaptation of the length of initial chemotherapy to the data given by plate-thermography. (Author abstract) (24 Refs)

22. CYSTOSARCOMA PHYLLOIDES OF THE BREAST: A NEW THERAPEUTIC PROPOSAL.

Contarini O, Urdaneta LF, Hagan W, Stephenson SE
2726 St. Johns Ave., Suite 5, Jacksonville, FL, 32205
Am Surg; 48(4):157-166 1982

An analysis of forty cases of cystosarcoma phylloides of the breast was undertaken to clarify the relationship between histology, surgical treatment and prognosis of this fibroepithelial tumor. Thirty-eight female patients 12 to 85 yr of age, treated for this diagnosis over a 17-yr period, were studied retrospectively. Histologically malignant lesions were diagnosed in 17 cases: 6 were treated by local excision, 1 by subcutaneous mastectomy with prosthetic implant, 4 by simple mastectomy, 3 by modified, 2 by radical mastectomy, and 1 by biopsy only. Of the 23 histologically benign tumors, 18 were treated by local excision, 3 had simple mastectomy, and 1 had subcutaneous mastectomy with prosthetic implant. Three recurrences, observed (7.5%) among patients with benign tumors, were locally excised. Wide local reexcision has controlled the disease to date after av follow-up of 32 mo. In the malignant group, metastases developed in four patients (10%). Three of these patients are dead of disease and one is being treated by chemotherapy. Malignant histology seemed to correlate directly to the presence of pain (46.6%), size of the tumor (av 7 cm in diameter), and older age (av 52 yr), but there was no correlation with prognosis. Recent reports on the subject advocate wide local excision for small benign lesions and simple mastectomy for larger or malignant ones. Our data indicates that the histologic appearance does not correlate with the clinical behavior of this neoplasm, and the choice of the procedure does not alter the long-term result, provided that the tumor is completely excised. More radical procedures than wide local excision are not justified for cystosarcoma phylloides which behaves more like a soft tissue sarcoma than a breast gland tumor. (Author abstract) (32 Refs)

SELECTED CASE HISTORY REPORTS (CLINICAL CORRELATIONS)

23. CARDIAC TAMPONADE DUE TO MALIGNANT PERICARDIAL EFFUSION IN BREAST CANCER: A CASE REPORT.

Almagro UA, Caya JG, Remeniuk E

Dept. Pathology, Veterans Admin. Medical Center, 5000 West National Ave., Wood (Milwaukee), WI, 53193

Cancer; 49(9):1929-1933 1982

Cardiac tamponade resulting from malignant pericardial effusion is an uncommon initial presentation of various extracardiac malignancies. Only 29 cases of extracardiac malignancies with this initial presentation have been previously published. Lung carcinoma leads as the most common malignancy involved, followed by carcinoma of the stomach, pancreas, kidney and ovary, mediastinal rhabdomyosarcoma, malignant lymphoma and leukemia. This report describes a case of breast carcinoma in a 47-yr-old woman who initially presented with cardiac tamponade. To the best of the authors' knowledge, no similar case has ever been reported in the literature. (Author abstract) (10 Refs)

24. GIANT ADENOFIBROMA OF THE BREAST IN A PREPUBERTAL GIRL: A CASE REPORT.

Leis HP, Sabatini MT, Cleary JB, Feiner H, La Raja RD, Makoon-Singh E

Dept. Pathology, Cabrini Medical Center, New York, NY

Breast; 8(1):13-17 1982

A case of giant adenofibroma of the breast in an 11-yr-old prepubertal girl is described. The patient presented with a mobile 8 cm mass in the right breast. An encapsulated tumor was removed surgically. Histological examination revealed a tumor formed by epithelial and stromal components encircled by overlapping layers of collagen. The tumor was positive for both estrogen and progesterone receptors. Giant adenofibroma of the breast can be distinguished from juvenile hypertrophy by the presence of a discrete, palpable mass and hormonal abnormalities. (20 Refs)

25. DIABETES INSIPIDUS AND BREAST CANCER.

Schear EA, Falko JM, Catalsnd S, Johnson J, Fanning W

(c/o Falko) Div. Endocrinology and Metabolism, Ohio Sate Univ. Hosp., 410 W. Tenth Ave., Room N-1111, Columbus, OH, 43210

South Med J; 75(3):354-356 1982

We have described a case of breast cancer resulting in symptomatic diabetes insipidus from a metastatic mass in the hypophyseal stalk, detected by CAT scan of the brain. Satisfactory symptomatic and biochemical resolution of the polyuria was achieved with chlorpropamide alone. (Author abstract) (10 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

26. MAMMOGRAPHIC FEATURES OF THE BREAST AND BREAST CANCER RISK.

Brisson J, Merletti F, Sadowsky NL, Twaddle JA, Morrison AS, Cole P

Dept. Social and Preventive Medicine, Laval U., Quebec City, Quebec, G1K 7P4, Canada

Am J Epidemiol; 115(3):428-437 1982

The authors conducted a case-control study at two Boston, Massachusetts area hospitals to evaluate the relation of anatomic features of the breast, visible on the xeromammogram, to the risk of breast cancer. The cases were 408 women with newly diagnosed breast cancer and the controls were 1,021 women without signs or symptoms of breast disease. The features of the breast assessed were the 'parenchymal pattern' as defined by Wolfe and specific radiologic characteristics which are components of the parenchymal pattern classification. Women whose mammogram showed the P2 or DY parenchymal patterns were at elevated risk compared to women with the N1 pattern. Further, risk increased regularly with increases in the percentage of the breast that showed nodular densities and with increases in the av size and concentration of these densities. Women with extensive homogeneous density were also at elevated risk. These findings were observed only among women aged 20-59 yr. In this group, women with nodular densities in 60% or more of the breast appeared to have a five-fold increase in risk compared to women without nodular densities in the breast. (Author abstract) (22 Refs)

27. THE RELATION OF MAMMOGRAPHIC FEATURES OF THE BREAST TO BREAST CANCER RISK FACTORS.

Brisson J, Sadowsky NL, Twaddle JA, Morrison AS, Cole P, Merletti F

Dept. Social and Preventive Medicine, Laval U., Quebec City, Quebec, G1K 7P4, Canada

Am J Epidemiol; 115(3):438-443 1982

The authors evaluated the relation of breast cancer risk factors to the appearance of the breast on xeromammograms. Subjects were 1,021 women without breast cancer whose first xeromammographic examination at one of two Boston, Massachusetts area hospitals was done for a reason described as 'baseline' or 'routine'. The principal mammographic features assessed were the percentage of the breast showing nodular densities and the percentage showing homogeneous density. The extent of nodular and homogeneous densities decreased as age increased. The amount of both types of density decreased with increase in the number of full-term pregnancies. The percentages of the breast showing nodular and homogeneous densities were slightly higher for premenopausal compared to postmenopausal women, and for women with a history of breast biopsy or aspiration compared to women without. Certain characteristics of observed relations between risk factors and mammographic features differed for the two types of densities. (Author abstract) (14 Refs)

28. EFFECT OF AGE AT FIRST CHILDBIRTH ON RISK OF DEVELOPING SPECIFIC HISTOLOGIC SUBTYPE OF BREAST CANCER.

LiVolsi VA, Kelsey JL, Fischer DB, Holford TR, Mostow ED, Goldenberg IS
Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar St., New Haven, CT, 06510
Cancer; 49(9):1937-1940 1982

Epidemiologic variables related to breast cancer risk were assessed in a case-control study of 332 women with breast carcinoma and 1,353 comparison women. Risk factors for breast cancer as a whole included nulliparity, late age at first childbirth, early age at menarche, late age at menopause, personal history of benign breast disease, family history of breast cancer, and among postmenopausal women, body weight. These risk factors were then analyzed with respect to histologic subtype of breast cancer involved, ie, duct-derived or lobular tumors, to determine whether the association between any of the risk factors and breast cancer varied according to histopathologic subtype. Histologic subtype for the 316 cases reviewed included 284 duct cancers and 32 lobular carcinomas. Although slight differences were noted among some of the risk factors and the variety of cancer, none of the differences was marked except for the variable age at first birth. For ductal carcinoma, the risk was highest among nulliparous women and decreased the younger a woman was at the time she gave birth to her first child. The risk of infiltrating lobular carcinoma, however, was lowest among nulliparous females or those who had given birth at a young age and increased the older a woman was when she gave birth to her first child. (Author abstract) (9 Refs)

29. STAGE-SPECIFIC BREAST-CANCER INCIDENCE RATES BY AGE AMONG JAPANESE AND CAUCASIAN WOMEN IN HAWAII, 1960-1979.

Ward-Hinds M, Kolonel LN, Nomura AM, Lee J
Epidemiology Program, Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI, 96813
Br J Cancer; 45(1):118-123 1982

We have analyzed the age- and stage-specific breast-cancer incidence rates of Japanese and Caucasian women in Hawaii for a 20-year period. A comparison of the 1,192 Japanese and 1,531 caucasian patients by stage at diagnosis showed that Japanese women were likely to have breast cancer diagnosed at an earlier stage than Caucasian women, but this difference was statistically significant only after the menopause (ages 55+). We further found that for age 50-74, the age-specific ratios of Caucasian to Japanese incidence rates were least for in situ breast cancer, and successively greater for localized, regional and distant breast cancer. We interpreted this latter finding to be an indication that postmenopausal breast cancers in Japanese women have slower average growth rates than in Caucasian women. Such slower growth rates may explain the better breast-cancer survival among Japanese women after allowing for differences in stage, tumor size, histology, or treatment. (Author abstract) (20 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

30. TUMOUR LOCALIZATION OF MONOCLONAL ANTIBODY AGAINST A RAT MAMMARY CARCINOMA AND SUPPRESSION OF TUMOUR GROWTH WITH ADRIAMYCIN-ANTIBODY CONJUGATES.

Pimm MV, Jones JA, Price MR, Middle JG, Embleton MJ, Baldwin RW
Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, NG7 2RD, England
Cancer Immunol Immunother; 12(2):125-134 1982

The tumor-localizing potential of Sp4/A4 monoclonal antibody to the rat mammary carcinoma Sp4 isolated from hybridoma supernatants was established and the therapeutic effectiveness of the monoclonal antibody conjugated to the broad-spectrum anti-tumor agent adriamycin (ADR) was assessed. Characterization of SP4/A4 is described. Following iv injection of 125I-Sp4/A4 antibody into normal WAB/Not rats, blood levels of the antibody dropped to 50% over the first 5 hr and then decreased more slowly, with a half-life of 40 hr. Urinary excretion averaged 18% of injected dose over the first 24 hr and showed similar rates over the next 3 days. Raised levels of Sp4/A4 were found in tumor tissue of rats with sc growths of SP4 as compared with lung, liver, spleen, kidney, and heart. The time course of 125I-Sp4/A4 uptake was examined. When rats bearing other tumors were included, levels of radioactivity in Sp4 tumor growths exceeded those in any of the organs examined, and the activity in other tumors was comparable to that in visceral organs. No preferential localization of 125-I-labelled normal rat immunoglobulin was observed in Sp4 tumors. Treatment of Sp4 tumor cells with Sp4-A4 antibody did not inhibit their growth in syngeneic rats; treatment of hosts with antibody similarly had no inhibitory effect on growth of an sc tumor challenge. Treatment of Sp4 cells with ADR-monoclonal antibody conjugates significantly retarded Sp4 tumor growth. The results indicated that monoclonal antibody directed against tumor cell surface antigens may be highly effective for tumor targeting of therapeutic agents. (22 Refs)

31. CYCLIC BIOLOGICAL EXPRESSION IN MOUSE MAMMARY TUMORS.

Kiang DT, King M, Zhang HJ, Kennedy BJ, Wang N
Section Medical Oncology, Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Science; 216(4541):68-70 1982

Biological characteristics were assessed in GR mouse mammary tumors during 22 serial transplantations. Although unidirectional progression from hormone dependency to independency was observed, other biological markers such as progesterone receptors, polyploid frequency, and thymidine kinase activity demonstrated cyclic phenomena every fourth to sixth transplant generation, suggesting the continued presence of regulatory mechanisms among various cell subpopulations. (Author abstract) (13 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Almagro UA 23
Amiel JP 21
Arcangeli G 20
Bailey RA 1
Baldwin RW 30
Barnes BC 11
Baum M 13
Benjamin RS 19
Benz C 14
Bettelheim R 18
Blumenschein GR 11
Blumenschein GR 19
Bodey GP 11
Boyd NF 3
Boyd NF 4
Brisson J 26
Brisson J 27
Buzdar AU 11
Cadman E 14
Campbell JE 3
Campbell JE 4
Cantwell B 16
Casey AJ 18
Cataland S 25
Caya JG 23
Cleary JB 24
Cocconi G 12
Cohen JL 6
Cole P 26
Cole P 27
Contarini O 22
Cooke G 3
Cooke G 4
Coombes RC 18
Cornillot M 5
Creton G 20
Cuschieri A 15
Danesi DT 20
Di Marco AR 17
Diebold P 21
Dormont D 21
Dowsett M 18
Duffy MJ 8
Embleton MJ 30
Ewer M 19
Falko JM 25
Fanning W 25
Feiner H 24
Fennelly JJ 16
Fischer DB 28
Fishell E 3
Fishell E 4
Fourrier E 10
Fraschini G 11
Freireich EJ 19
Fruet F 17
Gavel M 10
Germanson T 3
Germanson T 4
Giovannini M 17
Goldenberg IS 28
Gorins A 10
Hagan W 22
Hanna W 7
Heslinga JM 2
Heuson JC 12
Holford TR 28
Hortobagyi GN 11
Humphreys J 18
Izrael V 21
Johnson J 25
Jones JA 30
Jones M 16
Kadouche J 10
Kelsey JL 28
Kennedy BJ 31
Kiang DT 31
Kim K 1
King M 31
Kolonel LN 29
La Raja RD 24
Laurent J 5
Lee J 29
Legha SS 11
Legha SS 19
Leis HP 24
LiVolsi VA 28
Mackay B 19
Mackie CR 15
Makoon-Singh E 24
Merletti F 26
Merletti F 27
Middle JG 30
Mignot L 10
Mobbs BG 7
Morrison AS 26
Morrison AS 27
Mostow ED 28
Mouridsen HT 12
Nemeth E 6
Nervi C 20
Neville AM 18
Nomura AM 29
O'Briain DS 6
O'Sullivan B 3
O'Sullivan B 4
Palshof T 12
Pannuti F 17
Paridaens R 12
Pauwels EK 2
Pimm MV 30
Powles TJ 18
Preece PE 15
Price MR 30
Raam S 6
Revina JH 21
Remeniuk E 23
Reynier J 10
Rocchetta G 17
Rochet Y 10
Ross RJ 1
Rossi AP 17
Rotmensz N 12
Rozencweig M 12
Rubino I 17
Ryder DE 7
Sabatini MT 24
Sadowsky NL 26
Sadowsky NL 27
Salat-Baroux J 21
Schear EA 25
Schell FC 11
Simor I 3
Simor I 4
Stephenson SE 22
Sylvester R 12
Tamura H 6
Tattelman E 14
Taylor RE 18
Tehrani F 13
Thompson JS 1
Thorsen T 9
Tillis T 14
Trevoux R 10
Twaddle JA 26
Twaddle JA 27
Urdaneta LF 22
Van Oosterom A 12
Verhaeghe J 5
Verhaeghe M 5
Wallace S 19
Wang N 31
Ward-Hinds M 29
Wilson AJ 13
Wood RA 15
Yap HY 11
Yap HY 19
Zhang HJ 31
Zwaveling A 2
Zylberberg B 21

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SEPTEMBER, 1982

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS) 1-2
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS 3-5
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS 6-13
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS 14-18
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY) 19-50
- REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT 51-52
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY) 53-59

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HE 20.3173/2:

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. SINGLE OBLIQUE-VIEW MAMMOGRAPHY FOR PERIODIC SCREENING FOR BREAST CANCER IN WOMEN.

Lundgren B, Helleberg A
Mammography Dept., Gavle Hosp., S-801 17 Gavle, Sweden
JNCI; 68(3):351-355 1982

A population, originally 6,845 women, 40 years of age and over, was screened for breast cancer by single oblique-view mammography in 1974, and 1980. Of the 5,789 women remaining in their parish in 1980, 94% had attended the screening at least once. Of 111 breast cancers diagnosed in the 6.25-year study period, 78% were detected at screening, 15% as interval cancers, and 7% among nonresponders. Sixty-three percent of the women had tumors in clinical Stage I, and 59% had tumors less than or equal to 10 mm. The predictive value for biopsy recommendations by mammography was 78%. This method was considered very suitable for screening. In the older age groups there was probably some overdiagnosis of cancers that would never have become symptomatic. (Author abstract) (13 Refs)

2. EVIDENCE OF BREAST CANCER MORTALITY REDUCTION: AGGRESSIVE SCREENING IN WOMEN UNDER AGE 50.

Moskowitz M, Gartside PS
Dept. Radiology, Univ. Cincinnati Medical Center, Cincinnati, OH, 45267
AJR; 138(5):911-916 1982

Five year follow-up data for breast cancer screening of 10,531 self-selected women are presented. The data are compared with the Health Insurance Plan of New York population and it appears that the magnitude of the mortality reduction in these two populations is similar. However, contrary to the new York findings, the data demonstrate that the benefit to screening this population was maximal in women under age 50. No breast cancer deaths have been recorded in 5 years of follow-up in this younger population (6,030 individuals). Interpretation of the data is that aggressive screening for breast cancer can favorably alter breast cancer mortality, particularly in younger women. (Author abstract) (27 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

3. ABNORMAL NIPPLE ASPIRATE CYTOLOGY AND PROLIFERATIVE CHANGES ASSOCIATED WITH MALIGNANT BREAST DISEASE (MEETING ABSTRACT)

King EB, Chew K, Ernster VL, Barrett DL, Petrakis NL
Department of Epidemiology and International Health, University of California, San Francisco, CA
Acta Cytol (Baltimore); 25(6):721 1981

Satisfactory nipple aspirate cytology smears were obtained from 34 of 82 malignant breasts prior to surgery and evaluated for cellularity, the distribution of epithelial cells and cellular abnormalities. Tissue from each breast was reviewed indpendently and the histologic type of malignancy identified; the presence of benign lesions, including atypical epithelial proliferative disease (APD), was noted. Comparisons were made betwen these 34 malignant breasts, 61 breasts diagnosed as benign without APD and 39 breasts diagnosed as benign with APD. We found that women with abnormal cytology (moderate and marked atypical hyperplasia) have a 6.4 times greater risk of breast cancer than women with no cytologic abnormalities. Comparisons between the two benign groups showed that women with atypical cytology had a 3.6 times greater risk of APD than women with normal cytology. APD was present in 27 malignant cases (80%) and in 39 benign cases (39%). We also found that women with the cytologic finding of epithelial cells in papillary groupings had a 4.0 times greater risk of having brest cancer than women who had no papillary groupings on cytology. (no Refs)

4. PROSPECTIVE ASSESSMENT ON THE DIAGNOSTIC ACCURACY OF BREAST SCINTISCANNING, MAMMOGRAPHY AND IMMEDIATE CYTOLOGY IN BREAST DISEASE (MEETING ABSTRACT)

Wood RA, Preece PE, Duguid H, Hutchinson F, Wisbey ML, Neill G, Cumming JG, Clark J, Cuschieri A
University Department of Surgery, Ninewells Medical School, Dundee, Scotland
Br J Radiol; 58(11):812 1981

Following a report on the use of 99Tcm diethyline triamine penta acetic acid (DPTA) breast scintiscanning, it became necessary to evaluate prospectively this investigation against other diagnostic aids such as mammography and breast cytology. Patients attending a breast clinic were included in the study and this paper deals with the results obtained in 155 patients (age 17-93 years). Scintigraphic medial and lateral views of both breasts were obtained 1-2h after injection of 8mCi 99TcmDTPA iv, using a gamma camera. Mammography was performed with mediolateral and craniocaudal views. Aspiration cytology of the breast lumps were performed using the Diff Quik staining technique with immediate reporting. The results of the three investigations were reported blind using a scale 0-6. Breast cancer was confirmed histologically in 92 patients, 71 of whom were postmenopausal. When reported blind, mammography and DTPA breast scan have a low diagnostic yield for breast cancer in the premenopausal patients. However, the two tests are complementary in diagnosing breast cancer approaching that of cytology (95-100 per cent). Either test does not exclude breast cancer in the postmenopausal patient. (no Refs)

5. OBSERVER VARIATION IN THE INTERPRETATION OF XEROMAMMOGRAMS.

Boyd NF, Wolfson C, Moskowitz M, Carlile T, Petitclerc M, Ferri HA, Fishell E, Gregoire A, Kiernan M, Longley JD, Simor IS, Miller AB
Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
JNCI; 68(3):357-363 1982

We have examined variation in the interpretation of xeromammograms among radiologists designated to take part in a Canadian multicenter randomized controlled trial of screening for breast cancer. Radiologists read 100 xeromammograms comprising 10 histologically proved cancers, 40 benign abnormalities, and 50 normal films. Radiologists' opinions differed widely on the frequency of suspected or identified cancer. The diagnostic category 'suspicion of cancer' or 'cancer' was selected by radiologists for 10-55% of the films, and biopsy of aspiration was recommended for 21 to 53% of patients whose films were examined. Agreement on specific diagnostic categories was greatest for the diagnosis of cancer; agreement was least for the diagnosis of benign abnormalities and intermediate for the diagnosis of normality. Known cancers were in general correctly identified. These results indicate a need for development of methods to reduce observer variation in the interpretation of xeromammograms while preserving diagnostic sensitivity and validity. Results also emphasize the importance of developing strategies to ensure quality control in multicenter trials. (Author abstract) (11 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

6. ESTROGEN-INSENSITIVE PROGESTERONE RECEPTORS IN A HUMAN BREAST CANCER CELL LINE: CHARACTERIZATION OF RECEPTORS AND OF A LIGAND EXCHANGE ASSAY.

Mockus MB, Lessey BA, Bower MA, Horwitz KB
(c/o Horwitz) Dept. Medicine and Biochemistry, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Endocrinology; 110(5):1564-1571 1982

In modified culture conditions, T47D human breast cancer cells synthesize extraordinary amounts of progesterone receptors (PgR), but, unlike other progesterone target cells, the PgR are entirely independent of estrogen controls. In the present studies we characterize some physicochemical properties of the PgR in T47D cells. We also describe an exchange assay for cytoplasmic and nuclear forms of the receptors which has enabled us to demonstrate that after progesterone treatment, translocation is stoichiometric. Despite the anomalous regulation of PgR levels, these receptors are typical of steroid receptors; they sediment at 7-8S on sucrose density gradients, they bind ligands with high affinity (Kd approx 4 nM for R5020; Kd approx 2 nM for progesterone), they bind only progestins specifically, and they are thermolabile (t1/2 at 37 c is approx 15 min). Receptor levels range from 15-40 pmol/mg DNA, or more than 300,000 sites/cell. The ability of ligands to dissociate from and rebind to the receptors was measured and used in an exchange assay for nuclear PgR. The synthetic progestin R5020 dissociates readily from receptors (t1/2 approx 3 hr at 0 C and 1.5 hr at 10 C), and the dissociation of progesterone is even faster (t1/2 approx 30 min at 0 C). To quantify steroid exchange, receptor levels were measured in mixtures of hormone-filled and unfilled cytosols. These studies assess ligand dissociation and subsequent ligand rebinding. At 0 C for 4-18 hr or at 10 C for 4 hr, unlabeled progesterone dissociates from receptors, and R5020 rebinds all sites, resulting in 100% exchange. In contrast, despite the use of a variety of incubation times and temperatures, no more than 50% of receptors previously filled with R5020 can exchange for [3H]R5020. The progesterone to [H3]R5020 exchange assay was used to measure salt-extracted nuclear progesterone receptors. In cells treated for 5 min with 0.1 uM progesterone, all depleted cytoplasmic sites were quantitatively recovered from nuclei. These cells provide a new model system to study the molecular biology of human PgR. (Author abstract) (37 Refs)

7. STEROID HORMONE RECEPTORS AND SEX CHROMATIN FREQUENCY IN BREAST CANCER.

Smethurst M, Bishun NP, Fernandez D, Allen J, Burn JI, Alaghband-Zadeh J, Williams DC
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 OTL, England
J Endocrinol Invest; 4(4):455-457 1981

Seventeen primary breast tumors were divided into three groups according to the frequency of sex chromatin and subdivided according to the presence or absence of steroid receptors. Of the cytosol estrogen receptor positive tumors, only 3/15 showed a sex chromatin frequency of less than 10%. Of the tumors with frequencies of 11-20% or greater than 20%, 7/7 had estrogen and progesterone receptors, 6/7 had cytosol and nuclear estrogen receptors, and 6/7 had all three receptors. A possible association between the presence of steroid hormone receptors and sex chromatin frequencies of greater than 20% is suggested. (12 Refs)

8. ABNORMAL OXIDATIVE METABOLISM OF ESTRADIOL IN WOMEN WITH BREAST CANCER.

Schneider J, Kinne D, Fracchia A, Pierce V, Anderson KE, Bradlow HL, Fishman J
(c/o Fishman) Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Proc Natl Acad Sci USA; 79(9):3047-3051 1982

The three dominant oxidative biotransformations of estradiol were examined in 10 normal women and 33 females with breast cancer by using a recently devised radiometric method. Estradiol tracers, labeled with 3H specifically in the 17alpha, C-2, or 16alpha position, were used to measure both the rate and extent of 17beta-ol oxidation (the initial metabolic step) and the subsequent 2-and 16alpha-oxidative reactions. The mean +-SEM values for the extent of estradiol metabolism at these three specific sites were 76.9 +-5.3%, 31.1 +-4.0%, and 9.3 +-0.8%, respectively, in normal subjects. Corresponding data in patients with breast cancer - ie, 73.0 +-4.2%, 32.7 +-2.7%, and 14.9 +-1.5% - revealed a significantly greater extent of 16alpha-hydroxylation in the latter population. Because of the 16alpha-hydroxylated compounds (including estriol) are themselves potent estrogens, these changes may have important hyperestrogenic consequences that could have a bearing on the etiology of the disease. (Author abstract) (36 Refs)

9. PROLACTIN RECEPTORS IN HUMAN BREAST TUMORS.

Turcot-Lemay L, Kelly PA
Molecular Oncology Lab., Hotel-Dieu de Quebec, 11, Cote du Palais, Quebec GIR 2J6, Canada
JNCI; 68(3):381-383 1982

Prolactin-binding sites were determined in 759 human breast tumor biopsy specimens. Ovine prolactin (oPRL) was used in the binding assay of 659 tumors with 13% of the tumors showing a positive content with more than 1% specific binding. Human prolactin (hPRL) was utilized for 343 tumors with 36% of the tumors binding 1% or greater of the added radioactivity. When human growth hormone (hGH) was used as the labeled ligand in 95 tumors, only 2% of the tumors specifically bound more than 1% of the hGH. A total of 153 tumors were assayed simultaneously with the use of labeled hPRL and oPRL. Whereas 10.4% of the tumors showed the presence of prolactin-binding sites (greater than 1% specific binding) when oPRL was used, an approximately threefold increase (29.4%) in tumors possessing prolactin receptors was revealed when hPRL was used as the labeled ligand. Therefore, hPRL is the preferred ligand for the assessment of prolactin receptor levels in human breast cancer biopsy specimens. (Author abstract) (15 Refs)

10. CORRELATION OF THYMIDINE KINASE ACTIVITY, HISTOLOGY AND STEROID RECEPTORS IN PRIMARY BREAST CANCER (MEETING ABSTRACT)

Zhang HJ, Snover D, Kennedy BJ, Kiang DT
University of Minnesota, Minneapolis, MN, 55455
Proc Am Soc Clin Oncol; 1:C-29 1982

Tumor steroid receptor content and differentiation correlate with the recurrence rate of primary breast cancer. For predicting prognosis, we investigated another biological marker, thymidine kinase activity (TK) by the method of Breitman, as well as estrogen receptor (ER) by the DCC method and progesterone receptor (PgR) by the sucrose gradient method. Results were correlated in 48 primary breast cancer tissues. No correlation was found between TK and PgR in 38 tumors. When tumors were divided into ER-poor (less than 3 fmol), medium (3-30 fmol), and rich (greater than 30 fmol) groups, a correlation of TK with ER was found in the first two groups. High TK activity occurred in 71% (10/14) of ER-poor tumors, while only in 18% (3/18) of ER-medium tumors. In the ER-rich group, 9 of 16 tumors also contained high TK, probably resulting from 'hormonal stimulation.' In 33 tumors, detailed histological grade was analyzed by the method of Bloom and Richardson, and no correlation with TK was found. This study suggests that (1) ER-poor primary breast tumors usually have high TK and (2) high TK also exists in some of the ER-rich tumors. The significance of TK as a prognostic factor for disease recurrence and for response to chemotherapy warrants further study. (no Refs)

11. BIOCHEMICAL SUBGROUPING OF BREAST DISEASE (MEETING ABSTRACT)

Estes NC, Glover JL, Miller D, Watanabe A
Department of Surgery, Indiana University Medical Center, Indianapolis, IN, 46202
Proc Am Soc Clin Oncol; 1:C-28 1982

Although lymph node status and hormone receptor assay have been helpful additions, the prediction of biological activity of breast lesions remains a difficult problem. Minton has compared cyclic adenosine monophosphate (cAMP) measurements in breast tissue and has showed a progressive increase in the level of cAMP from normal to fibrocystic disease, with the highest level in breast cancer specimens. In the rat hepatoma system, Weber has shown an excellent correlation between increasing thymidine kinase (Tk) activity and increased tumor growth rate. We have conducted a feasibility study comparing cAMP and Tk as biochemical measurement of tissue proliferation in the human breast system. Tissue samples were obtained from breast biopsy or mastectomy specimens. All samples were immediately frozen and stored in liquid nitrogen until cAMP and Tk assays were done. Tk and cAMP activity was modeled after Weber and Steiner respectively. Tk levels were elevated in intraductal cancers with positive lymph nodes and negative estrogen receptors (3.3) but decreased when lymph nodes were negative and estrogen receptors were positive (1.9). We conclude that Tk shows improved correlation over cAMP in comparing breast lesions. Further studies are encouraged with the hope of improving predictability of biological behavior of breast lessions. (1 Ref)

12. SERUM FUCOSE IN STAGED BREAST-CANCER PATIENTS (MEETING ABSTRACT)

Cantwell B, Fennelly JJ, Ryan C
University College, Dublin and St. Vincent's Hospital, Dublin, Ireland
Br J Cancer; 44(2):287 1981

The concentration of protein-bound fucose in the sera of 144 normal subjects and 56 subjects with staged breast cancer was measured, in order to determine whether raised serum fucose levels in breast-cancer patients reflected tumor stage. The method used for measuring protein-bound fucose in the sera was that of Dische and Shettles as described by Winzler. Serum fucose levels were compared with concomitant estimate of CEA (carcinoembryonic antigen) and ESR (erythrocyte sedimentation rate) in breast-cancer patients and a positive significant correlation obtained. When compared to normal subjects significantly higher serum fucose concentrations were found in breast-cancer patients, and showed correlation with tumor stage but not specifically to axiliary-node status. In 6 of 7 patients with advanced breast cancer who had serial estimations of serum fucose, a falling level was noted in association with response to systemic treatments. These results suggest that significantly high serum fucose levels occur in breast cancer and correlate with advancing stage of disease but not with nodal status. Serum fucose estimations are also of value in assessing tumor stage and response to therapy in breast cancer. (no Refs)

13. RETINOIC ACID BINDING PROTEINS AND STEROID RECEPTOR LEVELS IN HUMAN BREAST CANCER.

Mehta RG, Kute TE, Hopkins M, Moon RC
Life Sciences Div., ITT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Eur J Cancer Clin Oncol; 18(3):221-226 1982

Samples of 31 human breast cancer tissues were examined for the presence or absence of cytosolic retinoic acid binding proteins (cRABP), estrogen receptors (ER) and progesterone receptors (PR). cRABP were detected as specifically sedimenting 2S components on sucrose density gradients. Specific binding under the 2S region for cRABP and under the 8S region for ER and PR were determined. The levels of cRABP ranged from less than 1 pmol to 14 pmol per mg of cytosol protein. Tumors containing less than 3 pmol cRABP were designated as low cRABP; tissues were considered ER- and PR- when the receptor levels were less than 10 fmol/mg protein. Approx 60% of primary and metastatic tumors examined contained high cRABP. Tumors with well differentiated histopathology exhibited increased levels of cRABP. There was no significant correlation between the presence or absence of steroid receptors and cRABP in human mammary tumors. (Author abstract) (25 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

14. SERIAL CARCINOEMBRYONIC ANTIGEN (CEA) IN METASTATIC BREAST CANCER (MBC) (MEETING ABSTRACT)

Mughal A, Hortobagyi G, Fritsche H, Buzdar A, Yap H, Blumenschein G, Swanson D
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-315 1982

One hundred sixty-seven patients (pts) with MBC were treated with combination chemotherapy including 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). All pts had plasma CEA determinations performed before FAC and serially thereafter. CEA levels were measured by a triple isotope, double antibody radioimmunoassay. The median follow-up was 15 months. Eighty-four pts had abnormal initial CEA values greater than 6 ng/ml (greater than 10 ng/ml for smokers). Forty-seven of 84 (56%) pts had complete response (CR)+ partial response (PR). All responding pts had gradual decrease in CEA levels. Response and remission duration (RD) were similar in patients with normal and abnormal CEA value. Nine patients had a rise in CEA level during initial 8 weeks of therapy. Repeat CEA level in 4 weeks decreased and all patients had clinical response. Pts in whom elevated pretreatment CEA levels returned to normal during therapy had longer RD (22 months) than responding pts in whom CEA did not become normal (8 months). Two consecutive CEA changes in the same direction correlated with response in 68 of 71 (95.7%) pts. Thirty-five of 38 pts who had progressive disease evidenced increasing CEA levels. Serial CEA level provided a lead time of 1 to 13 months (median 3 months) before clinical relapse was detected in 63% of pts. Two consecutive rising CEA values correlated with progression in 91.4% of pts. CEA is a useful marker for monitoring the clinical course of MBC. Early false rise in CEA level may occur with chemotherapy. Its use for early detection of progressive disease or as an additional criterion of response to systemic therapy makes it a valuable biologic marker. (no Refs)

15. CIRCULATING IMMUNE COMPLEXES (CIC) AND ASSOCIATED ANTIGEN IN BREAST CARCINOMA (BC) (MEETING ABSTRACT)

Salinas FA, Wee KH, Silver HK, Ragaz J
Cancer Control Agency of British Columbia and University of British, Columbia Vancouver, British Columbia V5Z 3J3, Canada
Proc Am Assoc Cancer Res; 23:986 1982

We have recently reported on tumor burden and its relationship to antigen concentration, size and composition of CIC in malignant melanoma and ovarian carcinoma. To further understand such interaction we evaluated CIC in 118 BC patients (pts) selected on the basis of objective measurable tumor burden. Pts were grouped as reported earlier: 50 Group (Gp) I pts with no evidence of disease at sampling time, 30 Gp II pts with minimal tumor burden estimated at 5 g, and 38 Gp III pts with known regional or distal metastatic disease. CIC were evaluated by following tests: Fetal liver cell (FLC), Raji-cell, and solid phase ClQ radioimmunoassays (RIA). Results of simultaneous evaluation showed a significant correlation among test results (r equals 0.84, p less than 0.01, Spearman test). Also significant was the mean +/- se, expressed as ug aggregated human IgG equivalent /ml serum (ug/ml), for FLC equals 32 +/-4, Raji equal 28 +/-4, and ClQ equals 26 +/-8, as compared to 95 normal control sera (11 +/-1). Elevated (mean + 2 SD) CIC were observed in 28/118 (24%), 27/118 (27%) and 5/15 (33%) by the FLC, Raji, and ClQ RIA respectively. BC pts demonstrated a non-linear relationship with tumor burden. From this study three elevated (10-fold) CIC samples were selected for breast cancer associated antigen (BCAA) isolation by a Raji-cell bound CIC method as reported earlier. Isolated BCAA depicted a common pI 5.0 for all Gp's with an extra band at pI 8.5 for Gp III serum. These results indicate that BCAA represents a proven source of specific biological molecules useful for developing clinical monitoring and diagnostic techniques for BC pts management. (1 Ref)

16. CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH METASTATIC BREAST CANCER (MEETING ABSTRACT)

Krieger G, Kehl A, Bause I, Kneba M, Nagel GA
Department of Hematology/Oncology, Medical University Clinics, D-3400 Goettingen, W. Germany
Proc Am Soc Clin Oncol; 1:C-9 1982

We report a prospective study designed to further evaluate clinical significance of circulating immune complexes (IC) as tumor markers and prognostic factors in patients (pts) with metastatic breast cancer (mbc). One hundred and ten pts with mbc are tested in 4 to 8 weekly intervals for the presence of serum IC using the C1q binding assay (Cba) and Raji cell radioimmunoassay (Rca). Results were correlated to prognostic factors and response to chemotherapy. Controls are 60 age matched healthy women and 71 pts with rheumatoid arthritis (RA). Currently the incidence of positive results (IC+) is 37% for pts with mbc, 56% for pts with RA, and 3% for healthy controls. Permanent IC elevation on repetitive measurements is found in 60% of the IC+ mbc pts. Mean IC levels are higher for mbc pts than for healthy controls but lower than for pts with RA. Results of Cba and Rca do not correlate in pts with mbc, in contrast to pts with RA. IC+ mbc pts differ from IC- pts in type of metastases (visceral metastases, IC+:52%, IC-:21%), menopausal status (prae- or peri- menopausal, IC+:56%, IC-:14%) and progressive disease (IC+:68%, IC-:39%). IC status does not predict chemotherapy responsiveness. Nine of 25 IC+ pts show a positive correlation between IC titers and change of tumor mass, 3 pts an inverse correlation (IC titers increase in remission). (no Refs)

17. RADIOIMMUNOASSAY AND ANALYTICAL DETECTION OF HUMAN MAMMARY EPITHELIAL ANTIGENS (HME-AGS) IN BREAST CANCER PATIENTS USING MONOCLONAL AND POLYCLONAL SPECIFIC ANTIBODIES (MEETING ABSTRACT)

Ceriani RL, Sasaki M, Blank EW, Peterson JA
Bruce Lyon Memorial Research Laboratory, Children's Hospital Medical, Center Oakland, CA, 94609
Proc Am Assoc Cancer Res; 23:1078 1982

HME-Ags were quantitated in the sera of breast cancer patients at different stages in their disease and later identified in the same sera by sensitive analytical procedures. HME-Ags are normal differentiation antigens found in human breast epithelial cells be they normal or neoplastic. Polyclonal and monoclonal antibodies have been prepared against them recently by us. The competitive radioimmunoassay (RIA) was sensitive down to 10 ng/ml and the identification of HME-Ags in the sera was carried out by affinity chromatography, separation and identification steps. High levels of HME-Ags were found by radioimmunoassay in breast cancer patients with disseminated disease and in a percentage of those with primary breast cancers. Normal women, men and patients with disseminated cancer of non-breast origin were negative. In support of these findings, HME-Ags were identified by the polyclonal and monoclonal antibodies in the serum of those breast cancer patients with high RIA values for HME-Ags, thus demonstrating the specificity of the assay. While polyclonal anti-sera identified the already described HME-Ags monoclonal antibodies identified a breast epithelial specific antigen with a molecular weight of 45K. (1 Ref)

18. BREAST CANCER SKIN TEST ANTIGENS OF INCREASED SENSITIVITY PREPARED FROM VESICULAR STOMATITIS VIRUS-INFECTED TUMOR CELLS.

Austin FC, Boone CW, Levin DL, Cavins JA, Djerassi I, Rosner D, Case R, Klein E
NCI, NIH, Westwood Building, Room 10A07, Bethesda, MD, 20205
Cancer; 49(10):2034-2042 1982

Crude membrane (CM) extracts were prepared from five cultured breast tumor lines (MDA-MB-157, MDA-MB-231, ZR75-1, HSO578T, and MCF-7) which had been infected with vesicular stomatitis virus (VSV) to augment their antigenicity. In skin test trials, CM extracts of uninfected MCF-7 cells elicited positive responses in 0 of 13 (0%) tests in breast cancer patients, while VSV-MCF-7 elicited positive responses in 11 of the same 13 patients (84.6%). CM extracts of VSV-ZR75-1 and VSV-MCF-7 elicited greater delayed hypersensitivity responses (mm induration at 48 hr) in breast cancer patients than in patients with lung carcinoma or melanoma. Although the sensitivity of VSV-ZR75-1 was too low (10 of 28, or 35.7%, of tests positive) to be useful as a skin test antigen, VSV-MCF-7 elicited positive responses in 30 of 38 (78.9%) tests in breast cancer patients, as compared to 2 of 15 (13.3%) and 2 of 13 (15.4%) of tests in patients with lung carcinoma and melanoma, respectively. The 'virus-augmented' CM extract of cultured MCF-7 cells exhibited markedly greater sensitivity as compared to control MCF-7 extracts (p less than .005), with a high degree of specificity for breast cancer patients as compared to patients with the other neoplasms (p less than .00001). The results of skin testing with VSV-MCF-7 CM extracts demonstrated antigenic cross-reactivity with a large number of breast cancer patients, a finding of great importance for any potential immunotherapy and/or immunodiagnosis. (Author abstract) (27 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

19. EFFICACY OF ORAL BCG THERAPY IN BREAST CANCER (MEETING ABSTRACT)

Serrou B, Cupissol D, Pujol H, Gary-Bobo J, Nguyen M, Gary-Bobo F, Favier F, Favier C
Department of Chemo-Immunotherapy, Centre Paul Lamarque, Montpellier 34 033, France
Proc Am Soc Clin Oncol; 1:C-339 1982

One hundred and forty breast cancer patients (T1 T3, N0-N1b) were treated by irradiation then randomized into two groups which received either no adjuvant therapy or 150 mg Immun BCG-F (Pasteur Institute) per os once a week for one year. Patients were subdivided and randomized by stage. Sixty patients were assigned to each of three subgroups: T2-N1, T1-N1, T3-N1. The study has since ended and all patients have been followed for at least 17 months. No side-effects were observed for the BCG group (vomiting, diarrhea, etc) which necessitated cessation of treatment. At 3 years, disease free survival time is significantly (p less than 0.05) increased for patients on immunotherapy. The results based on patient stratification show a significant amelioration for patients treated by BCG for those initially classed as T1-N1 or T2-N1. No significant difference was observed for the T3-N1 patients. It was previously noted that patients who relapse after immunotherapy ultimately respond better to chemotherapy. The group receiving BCG also demonstrated signs of immunorestoration: ameliorated hypersensitivity skin tests (p less than 0.05); increased numbers of autorosette forming cells (p less than 0.05), but no significant increase in natural killer activity. (no Refs)

20. PHASE II STUDY OF VINBLASTINE INFUSION IN THE TREATMENT OF REFRACTORY ADVANCED BREAST CANCER (MEETING ABSTRACT)

Shah MK, Creech RH, Catalano RB, Marie KS
Fox Chase Cancer Center, Philadelphia, PA, 19111
Proc Am Soc Clin Oncol; 1:C-280 1982

Twenty-one measurable disease patients with chemotherapy-refractory carcinoma of the breast were treated with continuous subclavian intravenous infusions of vinblastine at a dose of 1.6mg/m(2)/day for 5 days every 3-4 weeks. The 19 patients who lived more than 21 days were evaluable for response and toxicity. None of these patients had prior treatment with vinca alkaloids. Five patients responded; one complete (CR) and 4 partial (PR). One patient with extensive skin metastases had a CR for 6 months. PR occurred in 1 patient with liver metastases (1.5 months), in 2 patients with bone metastases (2.5, 1+ months), and in 1 patient with subcutaneous metastases (2+ months). Five patients had stable and nine had progressive disease. Toxicities in the nineteen evaluable patients included WBC 3-4.4 (5); WBC 2-2.9 (2); WBC 1.1-0.9 (2). Five patients had mild to moderate gastrointestinal side effects and 1 had moderate mucositis. Three patients had mild degrees of paresthesia, and three patients had mild alopecia. Complications related to the subclavian catheters during 68 courses of vinblastine included infection (1), phlebitis (1), and pneumothoraces (2). (no Refs)

21. THE PHARMACOKINETICS OF HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN THE THERAPY OF ADVANCED BREAST CANCER.

Blossey HC, Bartsch HH, Kanne D, Koebberling J, Nagel GA
Dept. Medicine, Univ. Goettingen, Robert-Koch-Strasse 40, Goettingen D-3400, W. Germany
Cancer Chemother Pharmacol; 8(1):77-81 1982

The pharmacokinetics of medroxyprogesterone acetate (MPA: 1.5 mg/day, po) was investigated in 16 patients with advanced breast cancer. Initial phase kinetics revealed two groups of patients differing in the time needed to reach the plateau state: a first group exhibiting steady plasma levels of MPA within 5 days and a second group whose plateau was reached after 2 wk of treatment. There was a broad intra- and interindividual variation of MPA plasma levels in the plateau state which were dependent neither on the frequency of MPA determination nor on the duration of observation. These variations are probably a result of individual differences in drug absorption, distribution, and metabolism. Mitomycin C, which was part of the therapy schedule, had no effect on the actual plasma concentrations or on the plateau state. The plateau concentrations were very sensitive to dose modifications; there was a rapid decrease in MPA plasma levels following dose reduction or cessation of therapy. The elimination kinetics showed two phases, with half-times of about 20 hr and 3-4 days. Of three different solvents (diethyl ether, petroleum ether, and benzene:isooctane) used for extraction of MPA in the absence of MPA metabolites, diethyl ether was the most efficient. There was an excellent linear correlation between determination in plasma and ether extracts over a wide range of concentrations, suggesting that direct plasma RIA without extraction may be valid for assaying MPA in pharmacokinetic studies. (35 Refs)

22. PHASE I AND PRELIMINARY PHASE II STUDY OF 7-HYDROXY-7-DESAMINO-MITOMYCIN (KD-0122) IN ADVANCED BREAST CANCER (MEETING ABSTRACT)

Majima H

Chiba Cancer Center Hospital, Chiba 280, Japan

Proc Am Soc Clin Oncol; 1:C-278 1982

Phase I was performed for biopsy proven, advanced, conventional therapy resistant breast cancer patients who had minimal life expectancy of four month duration. KD-0122 did not produce anorexia, nausea, vomiting or signs of bone marrow depression up to 200mg per body (5mg per kg) as a single iv administration. The limiting factors of KD-0122 were reversible bone marrow depression and renal function disturbance, when a cumulative dose reached to 20mg per kg or 800mg per body, accompanied with occasional permanent dental damage. Ten breast cancer patients underwent phase II study using 2mg per kg per week by iv administration. Two patients had CR (complete response) and another two patients had PR (partial response) in soft tissue lesions, without clinical signs of bone marrow or renal function disturbance in 10 weeks treatment. By above, this agent has definite response to breast cancer in soft tissue lesions without clinical signs of bone marrow depression or renal disturbances up to cumulative dose of 20mg per kg. Therefore, this agent considered to be extremely useful as a induction therapy against breast cancer patients who are refractory to conventional hormonal or chemotherapeutic agents. (no Refs)

23. CMF +/- LEVAMISOLE (L) BREAST ADJUVANT CHEMOTHERAPY: 5 YEAR ANALYSIS (MEETING ABSTRACT)

Hakes TB, Currie VE, Kaufman RJ, Kinne D, Oettgen H, Pinsky C

Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY, 10021

Proc Am Soc Clin Oncol; 1:C-319 1982

The MSKCC Breast Adjuvant Program entered 256 Stage II/III (+lymph nodes (LN) patients pts) post mastectomy between 3/76 and 3/80. Median follow-up is 48 mo with 28% followed over 60 mo. Pts were stratified for menopausal status and number of + axillary LN's and then randomized to 24 mo of Cyclophosphamide, Methotrexate, Fluorouracil (CMF) (Bonadonna) or CMF+L. Percentage CMF dose given, number of leukopenic episodes, amenorrhea, and quadrant of primary lesion were not correlated with DFS (disease free survival). ERP had no effect on DFS but was highly correlated with survival. Percentage ideal CMF dose given at 6, 12, 18 and 24 mo was 72, 65, 60, and 48% respectively and not correlated with DFS. Sites of recurrent disease include: 21% local, 21% regional, 41% systemic, and 17% local-systemic. Levamisole has not extended DFS or survival. (no Refs)

24. PHASE II STUDY OF VP16-213 (ETOPOSIDE) IN REFRACTORY METASTATIC BREAST CARCINOMA.

Schell FC, Yap HY, Hortobagyi GN, Issell B, Esparza L

Medical Breast Service, Dept. Medicine, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Cancer Chemother Pharmacol; 7(2/3):223-225 1982

A phase II trial compared VP16-213 as an intermittent 5-day bolus against a continuous 5-day infusion, randomized to 77 patients (30-74 yr old) with advanced breast carcinoma refractive to conventional combination chemotherapy. Median prior chemotherapy was 23 mo. Good risk patients received 70 mg/square meter (m2)/day either as a continuous infusion over 120 hr or as an intermittent daily bolus dose over 1 hr daily. Patients considered poor risk received the same schedule of VP16-213 but at a dose of 60 mg/m2. Treatment cycles were 21 days and dosage was escalated or de-escalated according to toxic effects. Of the 35 evaluable patients given intermittent bolus therapy, 5 achieved partial remission (PR), 3 had responses less than partial, 6 had stable disease, and 21 progressive disease. Of the 31 evaluable patients given infusion therapy, one achieved complete remission, 3 achieved PR, 3 had responses less than PR, 5 had stable disease, and 19 had progressive disease. The most frequent toxicity was myelosuppression, which was severe in approx 50% of patients. Nausea and vomiting were moderate with the intermittent schedule but were essentially absent in the infusion group. VP16-213 exhibited activity against refractory breast cancer in approx 23% of patients, with almost 15% achieving PR or better. VP16-213 warrants further investigation in chemotherapy combinations for patients with an early stage of breast cancer. (12 Refs)

25. AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER: EFFECTS OF DOSE ON HORMONE LEVELS AND RESPONSE (MEETING ABSTRACT)

Harris AL, Dowsett M, Smith IE, Jeffcoate S

Royal Marsden Hospital, London, England

Br J Cancer; 44(2):286 1981

Aminoglutethimide (AG), combined with hydrocortisone, is a useful drug in advanced postmenopausal breast cancer. It inhibits adrenal steroid synthesis and peripheral conversion of adrenal androgens to estrone. The minimum effective dose is unknown, the usual dose being 1 g/day, and side effects increase with AG dose. We have therefore studied 28 consecutive postmenopausal patients with advanced breast cancer and measured estrone levels before treatment, and after 500, 750 and 1000 mg daily, with 20 mg hydrocortisone twice daily. Dehydroepiandrosterone-sulphate (DHEAS), the main adrenal androgen, was also measured. Both hormones were measured by radio-immunoassay. There were no significant difference between 500, 750 or 1000 mg/day AG in effects on estrone or DHEAS. Twenty-six patients were assessable for response. Six of 8 responders had estrone less than 40 pM but only 2/18 non-responders had such levels. There was no difference in DHEAS suppression. These results show that increasing doses of AG above 500-750 mg did not suppress estrone further, and suggest that an extra-adrenal source of estrone is responsible for higher estrone in non-responders. AG could be combined with an anti-estrogen in this group of patients to try and increase their response. (no Refs)

26. POTENTIAL CARDIOTOXICITY OBSERVED WITH DIHYDROXYANTHRACENEDIONE (DHAD) CHEMOTHERAPY (MEETING ABSTRACT)

Schell FC, Yap HY, Blumenschien GR, Bodey GP
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-83 1982

DHAD is a promising new agent developed in an attempt to find a drug with a broad spectrum of activity and devoid of cardiotoxicity. DHAD was evaluated in a phase II clinical trial for refractory metastatic breast cancer. A very encouraging response rate was seen with 6 of 27 patients achieving complete or partial remissions. However, four of these patients developed congestive heart failure either during or after treatment under circumstances such that this drug may have been a contributing factor. Each of these patients had been previously treated with Doxorubicin to a total dose of at least 450 mg/M2. Three of the four patients had at least one additional risk factor including age of 65 or greater, left precordial radiation therapy, hypertension or other cardiac disease history, and prior treatment with other cardiotoxic drugs such as Mitomycin-C. In each of the four patients cardiac decompensation was documented by multiple techniques in addition to the clinical syndrome including echocardiography and/or dynamic nuclear cardiac scans. Unfortunately no patient had an endomyocardial biopsy performed and cardiac monitoring in the other patients in the group was patchy due to the fact that this was an unexpected finding. Although DHAD can not be incriminated directly in these episodes careful cardiac monitoring must be included in studies evaluating this potentially very active agent. (no Refs)

27. A CROSSOVER COMPARISON OF TAMOXIFEN AND AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER (MEETING ABSTRACT)

Harvey HA, Lipton A, White DS, Santen RJ, Boucher AE, Shafik AS, Dixon R
The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA, 17033
Proc Am Soc Clin Oncol; 1:C-306 1982

We have previously reported that Tamoxifen(T) and a regimen of Aminoglutethimide and Hydrocortisone (AG) are equally effective in the treatment of advanced breast cancer. This study compares the sequential use of T and AG in 66 postmenopausal patients with Estrogen receptor (ER)+ or ER unknown tumors. Thirty-four patients were treated initially with AG and when their disease was again progressive they were crossed over to T. Similarly, 32 patients received T until disease progression then, after an appropriate interval to observe for a withdrawal response, they were crossed over to treatment with AG. The response rate, complete response (CR)+ partial response (PR), in the group first receiving AG was 47% with 13% stabilizations and a mean duration of response of 18 months. When this group of patients received T as second therapy, the overall response rate (CR + PR) was 24% with 21% remaining stable and a mean duration of response of 13 months. Of 16 responders to AG, 5 subsequently responded to T and of 11 AG non-responders 2 benefited later from T. In a comparable group of patients treated initially with T, CR + PR was 28%, stabilizations 28% with a mean duration of response of 15 months. The CR + PR on AG as second therapy in this group was 19% and there were 22% stabilizations. Of the 9 responders to T, 4 responded later to AG and of 14 patients failing T initially, 1 had a PR on later therapy with AG. We conclude that objective responses to T and AG occur after progression on either as first therapy but that patients who fail to respond to AG seldom respond to T and vice versa. (1 Ref)

28. TREATMENT OF METASTATIC BREAST CARCINOMA USING A COMBINATION OF 5-FLUOROURACIL (F), ADRIAMYCIN (A), CYCLOPHOSPHAMIDE (C) AND TAMOXIFEN (T) (MEETING ABSTRACT)

Legha S, Blumenschein G, Hortobagyi G, Buzdar A, Yap H, Bodey G
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-299 1982

In order to evaluate the efficacy of hormonochemotherapy we treated 85 previously untreated patients (pts) with metastatic breast cancer using T for 8 weeks (wks) followed with a combination of FAC-T in the responders and FAC alone in T failures. FAC-T were used simultaneously in 9 pts because of life threatening disease. The median age of the group was 57 years (36 to 78) and 69 pts were postmenopausal. After 8 wks of T therapy, 25 pts showed objective evidence of tumor regression, 15 had stable disease, and 36 had progressed. T was continued in the 40 responding pts and chemotherapy was added using F 500 mg/m2 day 1 and 8, A 50 mg/m2 day 1, and C 500 mg/m2 day 1 IV. A was continued to a cumulative dose of 450 mg/m2 at which time methotrexate was substituted in its place and treatment continued for a total of 2 years. The complete response (CR) rate for the entire group was 33% and the CR+PR (partial response) rate was 81%. Median duration of response for the group was 20 mos (4-45+) and the median survival was 30.5 mos (range 4 to 45+ mo). Median duration of response in 49 pts treated with FAC-T was 23.5 mos compared to 13 mos for the FAC treated group. The median survival for the 49 T-responders was 39 mos compared to 20 mos for the T-failures. We conclude that CR rate, the duration of response, and survival of breast cancer pts treated with FAC-T is superior to our previous experience with FAC chemotherapy. (no Refs)

29. SEQUENTIAL COMBINATIONS OF CONTINUOUS INFUSION ADRIAMYCIN AND VINBLASTINE IN PATIENTS WITH METASTATIC BREAST CANCER (MEETING ABSTRACT)

Yap HY, Blumenschein GR, Barnes B, Schell F, Buzdar A, Hortobagyi G, Benjamin RS
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-300 1982

We have previously observed an improved therapeutic index when adriamycin or vinblastine was given as a continuous infusion in patients with metastatic breast cancer. To further improve results, we explored two sequential combinations of adriamycin and vinblastine given by continuous infusion. All patients had previously received combination chemotherapy with cyclophosphamide, methotrexate and 5-FU(5-fluorouracil) with or without vincristine and prednisone. In the first sequential combination 23 patients received a continuous 4-day infusion of vinblastine at 1.4 mg/m(2)/day followed by a 2-day continuous infusion of adriamycin at a dose of 25 mg/m(2)/day. There were 6 partial responses (PR) (26%) and 10 patients had stable disease (SD). The median time to disease progression for the responding patients was 18 weeks. Following these disappointing results, the sequence of drug administration was reversed. In this continuing study, the 2-day infusion adriamycin was given before the 4-day infusion of vinblastine. Among the first 26 evaluable patients, there were 2 CR, and 13 PR giving an overall response rate of 57%. Seven patients had SD. The median time to disease progression has not been reached for responding patients but is in excess of 20 weeks. Side effects observed with both sequential combinations were similar and tolerable. They include myelosuppression (predominantly granulocytopenia), mild nausea and vomiting, mucositis, alopecia and paraesthesia. These results suggest that the sequencing of drug administration may influence response rate and that the sequential combination of continuous infusion adriamycin followed by vinblastine is an effective regimen in the treatment of patients with metastatic breast cancer. (no Refs)

30. THREE YEAR RESULTS OF A RANDOMIZED TRIAL COMPARING CMF TO ADRIAMYCIN (ADM), VINCRISTINE (VCR), CYCLOPHOSPHAMIDE (CPM) AND 5-FLUOROURACIL (5-FU) (AVCF) AS ADJUVANT THERAPY FOR OPERATED N+ BREAST CANCER. A 'GROUP INTER-FRANCE' TRIAL (MEETING ABSTRACT)

Misset JL, Delgado M, Plagne R, Belpomme D, Guerrin J, Fumoleau P, Metz R, Mathe G
Institut de Cancerologie et d'Immunogenetique, 94800 Villejuif, France
Proc Am Soc Clin Oncol; 1:C-325 1982

Between May 1978 and May 1981, 226 patients from 8 French centers were treated for N+ breast cancer after local treatment, including primary surgery with axillary node dissection and optional radiotherapy (performed in 45% of the patients according to the standards of participating centers). Patients were randomized to receive 12 monthly cycles, either of Cyclophosphamide, Methotrexate, Fluorouracil (CMF) according to Bonadonna's schedule, or of the followng combination: ADM 30 mg/m2 IV day 1, VCR 1 mg/m2 day 2, CPM 300 mg/m2 IV or IM and 5-FU 400 mg/m2 IV or IM days 3, 4, 5, 6 (AVCF). Prognostic factors (age, number of involved nodes, menstrual status) were equally balanced within the two therapeutic groups and radiotherapy was performed in the same percentage of patients. After a three year follow-up, disease-free survival is significantly higher (Kaplan-Meier life table analysis and log rank test p equals 0.0015) for the AVCF group. No difference has so far been detected in survival. No difference can be detected according to performance of radiotherapy. AVCF patients received a significantly higher percentage of the protocol dose of drugs than the CMF patients (mean 88% versus 72%, p equals 0.001) which may partly account for the difference in the results. Although a much longer follow-up is needed to assess long-term beneficial and adverse effects of ADM, we can already conclude that an ADM-containing regimen significantly reduces the rate of short-term relapses when compared to CMF in operable breast cancer with positive nodes. (no Refs)

31. TAMOXIFEN (TAM) VERSUS AMINOGLUTETHIMIDE (AG) VERSUS COMBINATION TAM PLUS AG IN ADVANCED BREAST CARCINOMA (MEETING ABSTRACT)

Smith IE, Harris AL, Morgan MW, Gazet JC, McKinna JA
Royal Marsden Hospital, London, England
Proc Am Soc Clin Oncol; 1:C-338 1982

One hundred seventeen patients with advanced breast cancer were treated in a control randomized cross-over trial with either TAM 10 mg orally twice daily or AG 250 mg orally times daily with hydrocortisone 20 mg twice daily. Non-responding or relapsing patients were switched to the alternative therapy. Eighteen (30%) of the 60 patients treated with TAM achieved an objective response and a further (18%) achieved stable disease. Seventeen (30%) of the 57 patients treated initially with AG achieved an objective response and 13 (23%) achieved stable disease. For bone metastases, AG achieved a 35% objective response and a further 26% subjective pain relief (overall benefit 61%) compared with 17% and 17% (34%) respectively for TAM. Median response duration was 20 months for TAM and 16 months for AG (NSD). Side-effects for AG including lethargy, rash and depression were commoner than for TAM and treatment had to be stopped in 7% of AG treated patients compared with 0% for TAM. In cross-over studies, 6 out of 12 TAM responders after relapse achieved a second response to AG (50%) as did 6 out of 29 patients who initially failed to respond to TAM (21%). In contrast 0 of 11 patients relapsing after response to AG subsequently responded to TAM, and only 1 out of 18 AG non-responders responded to TAM (6%). In a sequential study in 62 matched patients treated with combined TAM plus AG the response rate of 37% was not significantly better than that for either agent used alone, nor is there any evidence so far of a longer response duration. In conclusion AG is as effective as TAM for advanced breast cancer and may be superior as second-line treatment. Combined AG and TAM appear to be no more effective than either agent alone. (no Refs)

32. INTRASTAGE PROGNOSTIC HETEROGENEITY: IMPLICATIONS FOR ADJUVANT CHEMOTHERAPY OF BREAST CANCER.

Black MM, Hankey BF, Barclay TH
Inst. Breast Diseases, Westchester County Medical Center, Macy Pavilion, Suite 1039, Valhalla, NY, 10595
JNCI; 68(3):445-447 1982

The precise role of the use of adjuvant chemotherapy in the treatment of primary breast cancer has been questioned by some clinicians. One of the most important questions regarding the use of adjuvant chemotherapy is the identification of appropriate patients to receive it. The presence of positive axillary nodes has been the determining factor for the evaluation of chemotherapy in clinical trials. The possibility that other factors should be considered in deciding on the routine use of chemotherapy is discussed here on the basis of data from breast cancer patients diagnosed in the Province of Saskatchewan, Canada, none of whom received chemotherapy as part of their primary treatment. The data illustrate the prognostic heterogeneity that exists among patients with negative axillary nodes and among patients with positive axillary nodes. The implications of such heterogeneity include the possibilities that some patients may not benefit from adjunctive chemotherapy and that some may actually be harmed by it. Specific procedures are described for the analysis of existing clinical trial data to determine whether there is any evidence that some patients may not have benefited from adjunctive chemotherapy. Additional clinical trials would have to be done to substantiate such observations. (Author abstract) (8 Refs)

33. A RANDOMIZED STUDY OF COMBINATION CHEMOTHERAPY VS CHEMO-IMMUNOTHERAPY WITH CORYNEBACTERIUM PARVUM (CP) IN METASTATIC BREAST CANCER: IDENTIFICATION OF A SUBGROUP WITH INCREASED REACTIVITY AND SURVIVAL (MEETING ABSTRACT)

Fritze D, Becher R, Mayr A, Senn HJ, Abel U, Bruntsch U, Queisser W, Jungi WF
Medizinische Universitatsklinik, D-69 Heidelberg, W. Germany
Proc Am Soc Clin Oncol; 1:C-318 1982

CP is a gram-positive anaerobic bacillus and a potent immunologic stimulant. A randomized multicenter study in patients with measurable metastatic breast cancer was conducted to determine the relative effectiveness and toxicity of monthly chemotherapy (Vincristine 1.0 mg/m2iv day 1, Adriamycin 50 mg/m2 iv day 1, Cyclophosphamide 150 mg/m2 day 2-6 six times, followed by 5-Fluorouracil 600 mg/m2 iv day 1, Methotrexate 30 mg/m2 iv day 1 and cyclophosphamide 150 mg/m2 po day 2-6 until progression was documented) vs the same chemotherapy plus CP (5 mg/m2 subcutaneous day 1). Of the 150 evaluable patients, 33 out of 76 (45%) had complete or partial response to chemotherapy alone compared to 36 out of 74 (49%) treated additionally with CP. The Kaplan-Maier curves of duration of remission and survival were virtually identical (Median survival 22.2 vs 21.1 months). The hematologic and gastrointestinal toxicity were also similar in the two study groups. However, 19 out of 74 (26%) patients developed skin ulcers following repeated injections of CP. These patients showed prolonged survival (p equals 0.002 log rank test). The local CP toxicity may be related to increased duration of remission and survival in patients with metastatic breast cancer. (no Refs)

34. ADJUVANT CMF IN BREAST CANCER: COMPARATIVE 5-YEAR RESULTS OF 12 VS 6 CYCLES (MEETING ABSTRACT)

Tancini G, Bonadonna G, Marchini S, Bajetta E, Valagussa P, Veronesi U
Istituto Nazionale Tumori, Milan 20133, Italy
Proc Am Soc Clin Oncol; 1:C-333 1982

In 1975 a randomized trial was initiated in women N+ (node-positive)) comparing 12 vs 6 cycles of Cyclophosphamide, Methotrexate, Fluorouracil (CMF) to evaluate the possibility of reducing the duration of adjuvant treatment without compromising the therapeutic effect of the multimodal approach. Patients and methods were detailed during the 3-year analysis. The accrual for postmenopausal women was discontinued in March 1977 because of the initial results of our first CMF study. As of October 1, 1981, 459 patients were evaluable for the actuarial 5-year analysis. Present results after 12 CMF are almost superimposable to those of the previous study (RFS (relapse free survival) 59.5%, Survival 78.4%) and therefore significantly superior to those of the control group (RFS 44.6%, Survival 66.2%). Our results also confirm that in both menopausal groups RFS was not significantly affected by estrogen receptor (ER) status. No CMF-induced leukemias were documented. Our findings are now sufficiently mature to indicate that the maximum tumor cytoreduction with CMF is achieved in a relative short period of time. To improve current results we are now testing a more complex and intensive form of the therapy (sequential vs alternating regimens) during the first 9 months postoperatively. (2 Refs)

35. RECYCLING PRIOR USED DRUGS IN SEQUENTIAL COMBINATION CHEMOTHERAPY (CT) ENHANCES RESPONSE AND SURVIVAL IN METASTATIC BREAST CANCER (MEETING ABSTRACT)

Rosner D
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-277 1982

During the past decade we have attempted to develop noncross-resistant regimens by recycling prior used durgs as potentiating agents to the newly added drugs in sequential regimens. In the present study a total of 176 patients [98 Estrogen Receptor (ER) (+) and (?) following hormonotherapy (HT) and 78 ER (-) without prior HT] were randomized to primary 2 or 3 drugs [Cytoxan (C), 5-Fluorouracil (F), +/- Prednisone (P)] followed sequentially at relapse or failure, by secondary 5-drugs [CFP-Methotrexate (M) Vincristine (V)] and Adriamycin (A) combination (CA) as tertiary CT. All these regimens used sequentially were effective and noncross-resistant. There were 48/89 (54%) responders in CF group; 52/87 (60%) in CFP primary CT; 36/78 (46%) in CFPMV secondary and 11/28 (39%) in CA tertiary CT. Median duration of remission was 11, 12, 8 and 10 months (m) respectively. The prior drugs C and F reused in secondary CT and again C in tertiary CT enhanced the drug effects of MV-P in CFPMV secondary and A in tertiary CA. In our prior studies MV-MVP and A alone used as secondary or tertiary line CT were significantly less effective (12%-13%-19%). The median survival for metastatic period in 89 patients receiving sequential CF-CFPMV-CA was 31.8m and 30.5m in 87 patients receiving CFP-CFPMV-CA. In a comparable group of 57 patients receiving CFPMV as primary CT the survival was lower (19.3m). (1 Ref)

36. A RANDOMIZED TRIAL OF HIGH DOSE 5-FLUOROURACIL (F), DOXORUBICIN (A), AND CYCLOPHOSPHAMIDE (C) VS CONVENTIONAL FAC REGIMEN IN METASTATIC BREAST CANCER (MEETING ABSTRACT)

Malik R, Blumenschein GR, Legha SS, Hortobagyi GN, Buzdar A, Yap HY, Hill S, Bodey GP

M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030

Proc Am Soc Clin Oncol; 1:C-303 1982

In order to evaluate the chemotherapy dose response relationship in patients (pts) with metastatic breast cancer, a randomized trial was conducted using a high dose FAC regimen in the protected environment with prophylactic antibiotics (PEPA) or conventional dose FAC. Sixty ambulatory pts free of detectable CNS metastasis were treated on the protocol. Thirty-two pts were randomized to be treated in PEPA and were given F 500 mg/m2 d 1-5, A 85 mg/m2 d 1 and C 1500 mg/m2 d 1 for 1st 3 courses. Twenty-eight pts in the control arm received conventional dose FAC as F 500 mg/m2 d 1 and 8, A 50 mg/m2 d 1 and C 500 mg/m2 d 1. All 60 pts subsequently received conventional FAC chemotherapy until a cumulative doxorubicin dose of 450 mg/m2 at which time methotrexate was substituted for Doxorubicin. The response rate complete response (CR) + partial response (PR) at the end of 1st 3 courses in the PEPA group was 70% vs 39% for controls. The overall response rate (CR+PR) was 84% for PEPA group and 82% for controls with complete remission rates being 34% and 32% respectively. Twenty-two out of 27 PEPA pts have relapsed with a median duration of 11 months (4-29+). Seventeen out of 23 control pts have relapsed with a median duration of response of 15 months (17-29+). The median duration of survival was 22 months for PEPA pts and 19 months for controls. Incidence of mucositis and fever was considerably higher in the PEPA group. There was no chemotherapy related death in either group. The advantage of higher response achieved at the end of 1st 3 courses in PEPA pts did not translate into longer duration of response or survival. High dose induction chemotherapy with FAC does not offer a significant advantage over conventional dose FAC for pts with metastatic breast cancer. (no Refs)

37. UPDATE OF DOXORUBICIN, DIBROMODULCITOL, AND MITOMYCIN-C (ADM) THERAPY OF METASTATIC BREAST CANCER RESISTANT TO CYCLOPHOSPHAMIDE, METHOTREXATE, 5-FLUOROURACIL, VINCRISTINE, PREDNISONE (CMFVP) (MEETING ABSTRACT)

Pinnamaneni K, Blumenschein GR, DiStefano A, Buzdar AU, YapHY
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-304 1982

Twenty-six evaluable metastatic breast cancer patients with demonstrated resistance to CMFVP or CMF chemotherapy were treated with Doxorubicin (A) 40 mg/m2 IV day 1, Dibromodulcitol (D) 70 mg/m2 po day 2-6. Mitomycin C (M) 10 mg/m2 day 1 was repeated on alternate 21 day cycles. A and D were given with each course. Predominant metastatic sites were visceral 54%, osseous 27%, soft tissue 19%. Sixty-five percent of patients had 1 to 2 metastatic sites. Thirty-one percent of patients had 3 metastatic sites. Four percent had greater than 4 metastatic sites. Four patients achieved complete remission (CR). Ten patients achieved partial remission (PR). Five patients were stable. Seven patients progressed. Median time to progression of CR + PR patients was 11 months. Median survival for responders was 18 months. Three of 4 CR patients remain alive and in CR after 31 months median follow-up. Responses were observed in visceral, osseous and soft tissue sites. Doxorubicin combination chemotherapy with D and M following CMF or CMFVP chemotherapy approaches the efficacy of front-line drug combinations for patients with previously treated metastatic breast cancer. (no Refs)

38. A RANDOMIZED ATTEMPT TO INCREASE THE EFFICACY OF CYTOTOXIC CHEMOTHERAPY IN METASTATIC BREAST CANCER BY HORMONAL SYNCHRONIZATION (MEETING ABSTRACT)

Lippman ME, Cassidy J, Wesley M, Young RC
Medicine and Biometric Research Branches, National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-305 1982

We have previously observed that human breast cancer (BC) cells in tissue culture can be growth inhibited by Tamoxifen (TAM) and that this inhibition can be reversed by estrogen (E). Others have used hormonal stimulation of BC cells in vitro to increase the efficacy of chemotherapy (CT). We asked whether TAM inhibition of BC followed by E reversal would increase the efficacy of CT. This question was approached in an ongoing trial in which 93 patients have been prospectively randomized to CT consisting of Cytoxan 750mg/m2 and Adriamycin 30mg/m2 on day 1 plus 5-FU (5-fluorouracil) 500mg/m2 and Methotrexate 40mg/m2 on day 8 (CAMF) vs the above CT plus TAM 20mg/m2 days 2-6 and Premarin 0.625mg Q 12H x 3 on day 7 (CAMFTP). CT was given in 21 day cycles. For the 90 evaluable patients, no differences exist for any important prognostic variables. No differences in percent of protocol CT administered or observed toxicity was seen between the two regimens. Objective response rate was nearly identical (62% vs 60% for CAMFTP). Prior adjuvant chemotherapy with L-Phenylalanine mustard (L-PAM) had no observable effect on response rate, duration or survival. Time to progression (13 vs 17 months) and survival (17 vs 23 months) of responders significantly favored the CAMFTP arm. Greater benefits of CAMFTP were seen in partial vs complete responders, perhaps because the latter group had a marked reduction in treatment intensity per protocol. While an additive effect of hormones plus CT cannot be entirely excluded as the explanation for the improved results with CAMFTP, our results suggest that further efforts to increase the efficacy of CT by perturbing tumor growth rates may be worthwhile. (no Refs)

39. 15 VS 30 WEEKS (WKS) OF ADJUVANT CHEMOTHERAPY FOR BREAST CANCER PATIENTS (PTS) WITH A HIGH RISK OF RECURRENCE: A RANDOMIZED TRIAL (MEETING ABSTRACT)

Henderson IC, Gelman R, Parker LM, Skarin AT, Mayer RJ, Garnick MB, Canellos GP, Frei E
Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Soc Clin Oncol; 1:C-290 1982

Pts entered on this trial between 8/74 and 6/81 were all considered to be at high risk either because they had 4 or more positive (pos) lymph nodes (185 pts) or a pos node in the highest axillary zone (15 pts). More than 1/4th had 12 or more pos nodes. Other pt characteristics: 15% less than age 40, 43% less than age 50, 48% premenopausal, less than 10% with lesions greater than 5 cm and 14% with lesions less than 2 cm in diameter. Chemotherapy consisted of a single IV injection of cyclophosphamide (C) 500 mg/M2 and Adriamycin (A) 45 mg/M2 every 3 wks. Twenty pts were randomized to receive either 5 courses (15 wks, 225 mg/M2 cumulative dose A) or 10 courses (30 wks, 450 mg/M2 A). There are no significant differences in the time to relapse among these pts given either 15 or 30 wks of C/A. Although the total accrual to this study limited to high risk pts is large and the follow-up substantial, the probability of declaring a difference if the true difference were one year or more in the median time to recurrence is still only 0.43. However, these data strongly suggest that there is no advantage to prolonged courses of adjuvant chemotherapy in the treatment of breast cancer. (no Refs)

40. THE VALUE OF REPEATING STEROID RECEPTOR ANALYSES IN THE ENDOCRINE TREATMENT OF BREAST CANCER (MEETING ABSTRACT)

Stewart JF, King RJ, Steiner R, Hayward JL, Rubens RD
Imperial Cancer Research Fund Breast Cancer Unit, London SE1 9RT, England
Proc Am Soc Clin Oncol; 1:C-283 1982

One hundred and fifty-six patients with advanced breast cancer of known estrogen receptor (ER) and progesterone receptor (PgR) status treated by endocrine therapy were studied. Regarding a value for both ER and PgR as greater than or equal to 5 fmol/mg cytosol protein as positive, patients were divided into 4 phenotypic sub-groups:- ER+PgR+ (43%), ER+PgR- (26%), ER-PgR+ (8%) and ER-PgR- (23%). Responses to first endocrine therapy for each tumor phenotype were ER+PgR+ 50%, ER+PgR-27%, ER-PgR+ 27% and ER-PgR-6%. Four of 16 (25%) patients with ER+PgR+ tumors responded to subsequent endocrine therapy, but responses were not observed for 20 tumors of any other phenotype. With ER+PgR+ tumors, responses were seen in 20/30 (67%) patients when receptors were measured on tumor recurrence or on primary tumor immediately before endocrine therapy; but in only 11/32 (32%) when receptor analysis was performed on primary tumor and endocrine therapy was started only after failure of primary local therapy. In sequential analyses of receptors a change in ER phenotype occurred in 28/104 (27%) tumors, and in PgR phenotype in 12/42 (29%). These results demonstrated that repeat steroid receptor assays immediately before endocrine therapy improve the prediction of response to treatment. (no Refs)

41. HORMONAL THERAPY IN THE MALE BREAST CANCER ADVANCED STAGES (MEETING ABSTRACT)

Kantarjian H, Yap H, Hortobagyi G, Buzdar A, Blumenschein GR, Eckles N, Ho DH

M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030

Proc Am Soc Clin Oncol; 1:C-314 1982

Hormonal therapy is an established modality of treatment in the advanced stages of female breast cancer. Between 1944 and 1980, 41 patients with advanced male breast cancer were treated with 5 different hormonal modalities. Previous response to hormonal therapy did not predict further hormonal response (48% in responders vs 51% in non-responders). The median survival from metastasis (SM) was 24 months with no significant difference between those who did (24 months) or did not (21 months) have orchiectomy. The median SM was 35 months in responders vs 12 months in non-responders to hormonal therapy. We conclude that hormonal manipulation is a useful palliative modality of treatment in the advanced stages of male breast cancer with low toxicity and morbidity, a good response rate and response duration. In a category where cure is not yet achievable, hormonal therapy deserves a trial prior to chemotherapy if no life-threatening organ involvement exists. (no Refs)

42. A PROSPECTIVE RANDOMIZED STUDY OF HORMONE-CHEMOTHERAPY WITH OR WITHOUT PSEUDOMONAS VACCINE (PV) IN METASTATIC BREAST CANCER (MBC) (MEETING ABSTRACT)

Hortobagyi G, Blumenschein G, Frye D, Yap Y, Schell F, Barnes B

M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030

Proc Am Soc Clin Oncol; 1:C-313 1982

One hundred fifty-four evaluable patients (pts) with MBC were treated with 5-fluorouracil, adriamycin and cyclophosphamide (FAC). Pts with estrogen receptor (ER)-positive or unknown tumors were also given tamoxifen (T) 6-8 weeks before starting FAC. All were randomized to treatment with (75) or without (79) PV. The median age was 57 yrs (range 30-75); median disease free interval: 24 months (0-180). ER status number of metastatic sites, menopausal status and dominant sites of disease were equally distributed in the PV+ and PV- groups. Thirty-four percent of 105 pts achieved a complete (CR) or partial remission (PR) after 6-8 weeks of T. Overall CR + PR, after T+FAC+/-PV was 84% (CR equals 29%): 65 of 75 (87%) with FAC +/- T and 65 of 79 (82%) with FAC +/- T+/-PV. Thirteen of 25 (52%) pts responsive to T achieved a CR after T+FAC+/-PV. In 11 pts who achieved only a PR after FAC, local therapy improved response to CR. After a median follow-up of 15 months less than 1/3 of pts have relapsed. Time to progression is projected to be significantly longer for pts responsive to both T and FAC (median greater than 23 months) than for pts responding only to FAC (16 months) or only to T (14 months). CR+PR and remission durations will be similar in FAC+PV and FAC groups. Gastrointestinal and hematologic toxicity were similar to our previous experience with FAC. PV induced fever, chills and local soreness in all pts. This combined modality therapy provides excellent palliation to pts with MBC. Improved CR and CR+PR rates have been achieved without significant added toxicity. (no Refs)

43. DOXORUBICIN AND CYCLOPHOSPHAMIDE ADJUVANT THERAPY OF NODE NEGATIVE BREAST CANCER (MEETING ABSTRACT)

Brooks RJ, Jones SE, Salmon SE, Chase EM, Davis SL, Moon TE, Giordano GF, Ketchel SJ

University of Arizona Cancer Center, Tucson, AZ, 85724

Proc Am Soc Clin Oncol; 1:C-327 1982

Although patients (pts) with node negative breast cancer, in general, enjoy a favorable prognosis following primary surgical management, almost 30% will eventually develop recurrent disease. This study was, therefore, undertaken in an effort to improve upon the treatment outcome presently available with local therapeutic modalities (surgery +/- radiotherapy) alone. Between 1975 and 1981, 97 pts with node negative breast cancer and primary tumors less than or equal to 5 cm in diameter (T1N0 or T2N0) were entered in a pilot study designed to evaluate the efficacy of a brief course of postoperative adjuvant therapy. Pts were treated with a combination of doxorubicin (Adriamycin), 30 mg/M2 IV day 1, and cyclophosphamide, 150 mg/M2 PO days 3-6, (AC) given at 3 week intervals. The initial study design called for all pts to receive 3 cycles of AC but following an early T2 relapse, the protocol was modified so that T2 pts would receive 8 cycles. Thus, 63 pts received 3 cycles of AC while 29 pts received 8 cycles. Five pts received less than the 3 prescribed courses of AC. To date, 4 relapses have occurred among the 97 pts receiving adjuvant AC (median follow-up is 44 months). Relapse free survival (RFS) approaches 95%. When compared to an historical control group matched for tumor size and nodal status, the difference in RFS is highly significant (p less than .001). Treatment was generally well tolerated. To date, no pt has manifested doxorubicin cardiotoxicity, however, 3 cases of second solid malignancies have been observed. While preliminary results are encouraging, further trials investigating this promising approach should be carried out in the context of controlled investigations. (no Refs)

44. LONG TERM COMPLETE REMISSIONS FROM CHEMOTHERAPY +/- HORMONAL THERAPY IN BREAST CANCER (BC) PATIENTS (PTS) (MEETING ABSTRACT)

Abramowitz J

M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030

Proc Am Soc Clin Oncol; 1:C-294 1982

Of an initial cohort of 619 pts with metastatic BC treated with 5-Fluorouracil, Adriamycin, Cyclophosphamide-Cyclophosphamide, Methotrexate, Fluorouracil (FAC-CMF) chemotherapy for at least 2 years, 116 went into complete remission (CR). Of these 116 pts, 81 had relapsed by 1979. Follow-up of these remaining 35 pts in CR showed that 18 had relapsed. Five patients with metastatic disease to supraclavicular lymph nodes also received radiotherapy to this area. These pts are still in CR 64 to 89 months from the start of chemotherapy. There are 12 pts that have maintained a CR after only chemotherapy +/- hormonal therapy. Eight of these 12 pts had undergone an oophorectomy before chemotherapy was started. Of these three pts had increasing disease prior to the start of chemotherapy, and for five pts an independent response to oophorectomy could not be evaluated. Median followup of these 12 pts is 74 months from the start of chemotherapy (range 53-86 months). All 12 pts are off all forms of therapy a median of 48 months (range 7-58 months). Sites of disease were bone marrow (2), chestwall (3), bone (4), lung and pleura (3), and lymph nodes (1). In certain pts aggressive therapy can lead to long term unmaintanined CR. (no Refs)

45. PROGNOSTIC IMPORTANCE OF PROLIFERATIVE ACTIVITY ALONE OR IN COMBINATION WITH ESTROGEN RECEPTORS (ER) IN NODE-NEGATIVE (N-) BREAST CANCERS (MEETING ABSTRACT)

Silvestrini R, Daidone MG, Bertuzzi A
Istituto Nazionale Tumori, 20133 Milan, Italy
Proc Am Soc Clin Oncol; 1:C-322 1982

Cell proliferative activity and hormonal receptor status represent potential markers of biologic aggressiveness. In fact the presence of ER (ER+) has been generally reported to be a good prognostic factor as well more recently the proliferative activity (3H-Thymidine Labeling Index, LI) proved to be a potential indicator of disease free survival (DFS) in patients with N- tumors. With the present study we proposed to confirm our previous finding about the relation between LI of primary tumor and probability of DFS. The results at 5 years on about 160 patients with N- tumors stressed the significantly higher (p less than 0.05) probability of DFS in patients with slow proliferative tumors (90%) than in those with fast proliferating ones (72%). The significant difference (p less than 0.05) in DFS was also conformed for premenopausal patients (39% for high vs 88% for slow proliferative tumors). The prognostic relevance of the presence or absence of ER and low or high proliferative activity in different association was analyzed in a more recent series of 116 patients with a median follow-up of 30 months. The probability of 3 years DFS was significantly higher (p less than 0.025) for patients with ER+ and slow proliferating tumors (93%) than for those with ER- and fast proliferating tumors (73%). Intermediate probabilities of DFS were observed for the tumors with the other ER/LI combinations. The possible improvement of prognostic assessment by the combined ER/LI associations in comparison with the parameters singularly analyzed will be discussed. (1 Ref)

46. ADJUVANT RADIOTHERAPY (RTX) WITH AND WITHOUT CHEMOTHERAPY (CHTX) FOR STAGE II BREAST CANCER (BC): A NATIONAL RANDOMIZED STUDY (MEETING ABSTRACT)

Biran S, Brufman G, Robinson E, Borovik R, Brenner H, Rath P
Department of Oncology, Hadassah University Hospital, Jerusalem, Israel
Proc Am Soc Clin Oncol; 1:C-320 1982

The aim of this study is to determine the effect of postoperative RTX with and without CHTX in stage III BC. One hundred thirty-three patients (pts) were randomized to receive: (a) post-operative RTX + CHTX with 1-phenyl-alanine mustard and 5-fluorouracil (L-pam + 5-FU), (b) CHTX alone (L-pam + 5-FU), (c) RTX alone, and (d) CHTX + RTX (1 course L-pam + 5-FU, followed by concomitant RTX and same CHTX). The overall 4 year survival was 83%. The overall relapse free survival (RFS) was 71%. THe RFS was 82% for pts receiving RTX and CHTX (groups a and d), 80% for CHTX alone (group b), and 53% for RTX alone (group c). RFS was similar in pre- and postmenopausal pts. Pts with no involved nodes had a better RFS than those with 1-3 nodes and 4 or more nodes (84%, 64%, and 67% respectively). RFS of pts receiving CHTX was better when greater than or equal to 85% of the planned dose was given compared with dose levels between 66-84% and less than or equal to 65% (79%, 75%, and 61% respectively). The delay in onset of CHTX up to 120 days did not have an influence on RFS, but a delay of greater than 120 days resulted in a lower RFS (79% and 63% respectively). The local recurrence rate was 2.9% for group a and d pts, 3.1% for group c, and 5.7% for group b pts. RFS was similar in pts who received RTX immediately after surgery (group a), or when CHTX was administered before RTX (group d). The lowest RFS was observed in pts who received RTX alone. The addition of RTX to CHTX did not influence the tolerance to CHTX, and also did not result in a deleterious effect on RFS. (no Refs)

47. THE INFLUENCE OF PRIMARY BREAST CANCER TREATMENT - MASTECTOMY (M) OR EXCISIONAL BIOPSY PLUS RADIATION (E+RT) - ON THE ABILITY TO DELIVER ADJUVANT CHEMOTHERAPY (C) (MEETING ABSTRACT)

Lichter AS, Lippman ME, De Moss EV, Edwards B, D'Angelo T, Gorrell C
National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-312 1982

We questioned whether treating primary breast cancer with E+RT would diminish the ability to administer C. Thirty patients have received C for breast cancer after treatment with M (17) or E+RT (13). Twenty-four were part of a randomized trial comparing M versus E+RT while 6 were treated off study concurrently with the randomized group. C consisted of Adriamycin (A) (30 mg/m2-day 1) and cyclophosphamide (CY) (150 mg/m2 po -day 3,4,5,6) administered every 28 days for 11 cycles except for a planned 49 day gap between cycle 1 and 2. Patients were treated with identical rules for dose reductions and escalations based on total white blood cell (WBC) and platelet counts. RT patients received significantly less CY (107% vs 95% of protocol dose) but not less A because escalations permitted for CY but not A led to M patients receiving greater than 100% of the initial dose in 5 of 11 cycles. WBC counts were lower for E+RT patients, especially early in their treatment when they were receiving RT. This count difference is explained almost totally by a lymphopenia in the RT group-neutrophil counts were similar in both groups. Dose reductions occurred in more E+RT patients (9/13) than M patients (6/17) but 3 RT patients had reductions in the first 3 cycles and could be re-escalated in subsequent cycles. We concluded that C can be safely give to patients undergoing E+RT for breast cancer essentially in full protocol doses. When patients are treated to limiting myelosuppression, E+RT patients apparently have some decrease in marrow reserve. Dose reductions should be based on absolute neutrophil count, not total WBC. (no Refs)

48. HEPATIC ARTERY INFUSION (HAI) IN METASTATIC BREAST CANCER (MEETING ABSTRACT)

Moorhead EL, Potchen M, Borst JR, Pawl LR, San Diego E, Dykstra CJ, Murray TV
The Grand Rapids Oncology Group, Grand Rapids, MI, 49506
Proc Am Soc Clin Oncol; 1:C-291 1982

HAI has been evaluated with varying success in the treatment of primary and selected metastatic malignancies involving the liver. HAI has not been extensively studied in metastatic breast cancer, a chemotherapeutically sensitive malignancy--which most often involves multiple sites. Following a dramatic result in one case, we have employed HAI as a part of the total treatment strategy (concomitant hormone therapy) for 17 patients with metastatic breast cancer. Maximum dose of HAI was 15 mg/kg of 5-Fluorouracil (limit 1,500 mg/day) given beteeen 5-10 days (as tolerated) and repeated monthly for a maximum (rarely reached) of 8 doses. Five out of ten patients who had failed on previous therapy demonstrated a PR (partial response) with a median survival of 13 months (2-20+ months) for response vs 4 months for no response (3-10 months). One patient is still alive at 20 months. There was one treatment related death. In 7 patients, HAI was employed as a part of the initial treatment of their metastatic disease. Seven out of seven demonstrated PR with a median survival of 17+ months (projected maximum 21 months) and a range of 5-64 months. Six out of seven patients survived 12 months with two still living at 16 and 17 months. We believe that HAI may be a useful palliative technique in metastatic breast cancer. We suggest a large scale study to test systemic vs HAI cytotoxic chemotherapy, with appropriate concomitant hormonal therapy, in metastatic breast cancer with significant liver involvement. (no Refs)

49. REGIONAL CONSOLIDATIVE THERAPY FOLLOWING SYSTEMIC CHEMOTHERAPY IN METASTATIC BREAST CANCER (MEETING ABSTRACT)

Buzdar A, Blumenshein GR, Montague ED, Powell KC, Hortobagyi GN, Yap HY
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-286 1982

Twenty selected metastatic breast cancer patients after achieving maximum response with combination chemotherapy (fluorouracil, adriamycin and cyclophosphamide) were given consolidative therapy with irradiation and/or surgery to previous known sites of metastasis. The median age of the group was 48 yrs (range 29-64), and median number of sites of metastasis was 1 (range 1-4). The dominant sites of metastasis were soft tissue in 9 patients, visceral in 4 and bone in 7 patients. The consolidative therapy employed consisted of radiation therapy in 15 patients, surgery in 3 patients, and a combination of surgery of surgery and irradiation in 2 patients. Eleven of 20 patients were still in remission at 42+ months (6+ -84+), and 9/20 patients have developed recurrent disease. The median duration of response in relapsing patients was 32 months (17-54 months). Six patients recurred at the initial sites of disease, 1 failed in the brain and 2 had metastatic disease outside the areas of consolidative therapy. The dominant site of metastasis were soft tissue in 6 patients, visceral in 2 and bone in 2 patients who have continued in remission. These preliminary data suggest that consolidative therapy could significantly prolong the duration of response in selected metastatic breast cancer patients following chemotherapy and merits further evaluation. (no Refs)

50. PRELIMINARY RESULTS OF PRIMARY SYSTEMIC CHEMOTHERAPY IN ASSOCIATION WITH SURGERY OR RADIOTHERAPY IN RAPIDLY PROGRESSING BREAST CANCER.

Mourali N, Tabbane F, Muenz LR, Bahi J, Belhassen S, Kamaraju LS, Levine PH
(c/o Levine), NCI, NIH, Landow 1D-12, Bethesda, MD, 20205
Br J Cancer; 45(3):367-374 1982

One hundred twelve Tunisian patients with rapidly progressing breast cancer (RPBC) were entered into a clinical trial evaluating combination chemotherapy as a primary form of treatment before surgery or radiotherapy. Three cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) were administered at monthly intervals; patients were then randomized to surgery or radiotherapy to control the primary tumor, and 12 more cycles of CMF followed local/regional therapy. RPBC was sensitive to CMF; after only three cycles, 11% of evaluable patients showed complete remission and 78% had at least 25% diminution in tumor size. The disease-free interval (DFI) was substantially greater in this series than in a previously reported series treated by surgery and/or radiotherapy alone. No difference in DFI was found between patients randomized to receive surgery and those randomized to receive radiotherapy. Postmenopausal patients responded to CMF as well as premenopausal patients. Combination chemotherapy appears to play an important role in the control of RPBC, an aggressive malignancy often resembling inflammatory breast cancer. (Author abstract) (11 Refs)

REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT

51. THE PREDICTION OF EARLY RECURRENCE AFTER MASTECTOMY FOR BREAST CARCINOMA (MEETING ABSTRACT)

Nixon SJ, Steele R, Macgregor J, Hawkins RA, Forrest AP
University Department of Clinical Surgery, Royal Infirmary, Edinburgh, Scotland
Br J Surg; 68(11):802 1981

Previous studies which have identified patients at high risk of early recurrence have required radical mastectomy and/or internal mammary node exploration. Data relating tumor size, axillary node status, histological grade and estrogen receptor to major recurrence within 2 years of mastectomy were obtained from the literature and a computer program using Bayes' theory was written to calculate the probability of 2-year recurrence. These factors were recorded on 240 patients who underwent mastectomy and pectoral node sampling for invasive carcinoma. A computer-derived probability of recurrence was calculated for each patient. The computer program accurately predicted the recurrence rate for each independent risk factor and also for these factors in combination. The predictions for the whole group and for patients at high risk, medium risk and low risk were also very accurate. A simple score of the four risk factors was calculated for each patient. Only 1 of 47 patients with no risk factor (2 per cent) has recurred within 2 years of mastectomy, 21 of 145 with one or two risk factors (14 per cent) and 29 of 48 patients with three or four risk factors (60 per cent). Both the scoring system and the computer program could identify a group of patients at far higher risk of early recurrence than axillary node status alone. (2 Refs)

52. PSYCHOLOGICAL IDENTIFICATION OF BREAST CANCER PATIENTS BEFORE BIOPSY.

Wirsching M, Stierlin H, Hoffmann F, Weber G, Wirsching B
Dept. Basic Psychoanalytic Res. and Family Therapy, Psychosomatic Clinic, Heidelberg Univ., Moenchhofstr. 15a, 6900 Heidelberg, W. Germany
J Psychosom Res; 26(1):1-10 1982

Eight separate key psychological variables (interviewer/patient interaction, expression of emotions, rationalization, anxiety, hopelessness, helplessness, altruism, harmonization) were evaluated in 56 patients admitted for biopsy of a breast lump. Each of the eight variables was assessed on a 5-point rating scale by an initial interviewer and an independent rater; all interviews occurred 1 day before biopsy. Women who were later diagnosed as having malignant disease were rated significantly differently on all eight scales from women who had benign nodes. Denial, hopelessness, and altruistic behavior were among the predominant characteristics of the women with breast cancer. Interviewers and independent raters were successful in predicting the existence of malignancy in 83% and

94% of the cases, respectively. The comparatively extreme responses of breast cancer patients on most of the scales seem to be normal responses to an extremely stressful life situation. The significance of the patterns in terms of emergence and development of breast cancer was difficult to assess. (12 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

53. MODULATION OF 5-FU METABOLISM IN HUMAN MCF-7 BREAST CARCINOMA CELLS.

Major PP, Egan EM, Sargent L, Kufe DW
(c/o Kufe) Div. Pharmacology, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
Cancer Chemother Pharmacol; 8(1):87-91 1982

A previously reported relationship between the incorporation of 5-fluorouracil (5-FU) into total cellular RNA and loss of clonogenic survival in the human MCF-7 breast carcinoma cell line was studied in cells exposed to 5-FU and modulating agents such as N-(phosphonacetyl)-L-aspartate (PALA), methotrexate (MTX), and 6-methylmercaptopurine riboside (MMPR). Cells were grown in log phase and PALA (0.01, 0.10, and 1.0 mg/ml) and MTX or MMPR (concentrations of 10(-5)-10(-7) M) were added. Incorporation of 3H-FU and 32P into MCF-7 nucleic acids was measured, intracellular phosphoribosylpyrophosphate (PRPP) was determined, and clonogenic survival of MCF-7 cells was examined. Intracellular levels of PRPP were increased in the cells with the addition of PALA, MTX, and MMPR, while little if any significant increase in the absolute amount of FU incorporated into RNA was observed. The combination of PALA/MMPR resulted in the greatest absolute increases in formation of (5-FU)RNA (almost 2x control values). However, since PALA, MTX, and MMPR inhibit RNA synthesis, the absolute amount of 5-FU incorporated would not reflect the frequency of 5-FU substitution for uracil. In the presence of the modulating agents, the [3H]FU/32P ratio correlated better with loss of MCF-7 clonogenic survival than did the absolute amount of 5-FU incorporated in RNA. The [3H]FU/32P ratio may be useful for monitoring effects of other modulating agents on the metabolism of 5-FU. The relationship between (5-FU)RNA formation and loss of clonogenic survival should be corrected for the amount of newly synthesized RNA when 5-FU is combined with modulating agents that alter rates of RNA synthesis. (12 Refs)

54. A NEW MARKER FOR HORMONAL RESPONSIVENESS OF RAT MAMMARY TUMORS (MEETING ABSTRACT)

Liu DK
Department of Pharmacology, Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA, 17033
Proc Am Assoc Cancer Res; 23:910 1982

We previously reported a mammary-specific, Ca++-stimulated ribonuclease (Ca++-RNase) whose activity in normal mammary gland parallels the degree of differentiation. To determine whether this enzyme can serve as a marker for hormonal responsiveness, we have assayed the activity in a series of rat mammary tumors of varying orgin. RNase activity of an ammonium sulfate extract prepared from whole tissue homogenate was assayed under various ionic conditions, using (3H)poly(U) as substrate. Although the rate of poly(U) degradation varied according to the ionic conditions of the assay for a given tumor extract and also between tumor extracts under the same assay conditions, a general pattern emerged. In MT/9, MT/9a, DMBA 1, DMBA 8, DMBA 14 and R3230AC tumors, the activity assayed in the presence of CA++, or Ca++ plus EDTA, reflecting Ca++-RNase activity was 4 to 5 times higher than the activity assaysed with Mg++ and 100 to 700 times that in the presence of EDTA alone. These tumors are all known to be estrogen-responsive mammary adenocarcinomas. High Ca++-RNase activity was also present in the estrogen-sensitive 3M2N squamous cell carcinoma. Conversely, RNase activity assayed with Ca++ present was lower than that with either Mg++ or no added ion in MAMF2-TC, SMT-2A and 13762 mammary tumors, all undifferentiated, poorly differentiated or estrogen unresponsive mammary carcinomas. The same is true for mammary fibroadenomas. These results show that Ca++-RNase, which is easily detected in crude tumor extracts, is a useful marker in characterization of rat mammary tumors with respect to estrogen responsiveness. (no Refs)

55. IN-VIVO TAMOXIFEN-INDUCED ESTROGEN RECEPTOR TRANSLOCATION AND PROCESSING CORRELATED WITH BLOOD AND TISSUE TAMOXIFEN (TAM) LEVELS IN HUMAN BREAST CARCINOMA (MEETING ABSTRACT)

Kirby R, Fabian CJ, Tilzer L, Meltzer N, Sternson L, Stephens RL
University of Kansas Medical Center, Kansas City, KS, 66103
Proc Am Assoc Cancer Res; 23:941 1982

Following the initiation of TAM therapy at 10mg/M2 Q 12 hrs we measured serial values of unbound cytoplasmic estrogen receptor (ERc), bound nuclear estrogen receptor (ERn), and unbound cytoplasmic progesterone receptor (PgR) in 2 patients (pt) with breast carcinoma. Values were obtained from sequential biopsy of histologically-confirmed cutaneous metastases by the dextran-coated charcoal method. Simultaneous blood and tissue TAM levels were determined by high pressure liquid chromatography with fluorescence detection. Neither pt had an objective clinical response. Observations are: 1) a blood TAM level of approx 50ng/ml was adequate to initiate translocation of ERc, 2) the initial translocation of ERc occurred within 6-30 hrs of TAM, and 3) the complete processing of ERn occurred between 2-4 weeks of starting TAM. (no Refs)

56. MITOGEN-INDUCED BLASTOGENESIS AND RECEPTOR MOBILITY INHIBITION BY BREAST CANCER SERUM WITH ELEVATED OROSOMUCOID (ALPHA1-ACID GLYCOPROTEIN) LEVELS.

Cheresh DA, Distasio JA, Vogel CL, Lopez DM
(c/o Distasio) Dept. Microbiology D4-4, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
JNCI; 68(5):779-783 1982

Sera from cancer patients have been shown to suppress normal lymphoid cell responsiveness in vitro. In the present study, sera from breast cancer patients were demonstrated to be inhibitory to the concanavalin A (Con A)-, Proteus vulgaris-derived phytohemagglutinin-, and pokeweed mitogen-induced blastogenic responses of normal lymphoid cells. Orosomucoid (OR) (alpha1-acid glycoprotein), an acute-phase reactant, was elevated in these sera, and a positive correlation existed between the OR level in the sera and its immunosuppressive capacity. When normal lymphoid cells were reacted in fluorescein isothiocyanate-labeled Con A, cells that had been preincubated in breast cancer sera known to contain an elevated level of OR showed a significant decrease in Con A receptor mobility as compared to the receptor mobility of the same lymphoid cells preincubated in normal sera. Thus a component(s) from the sera of breast cancer patients had the capacity to inhibit lymphocyte activation. This inhibition might have resulted from an interaction of OR with the cell membrane. (Author abstract) (34 Refs)

57. DEVELOPMENT AND BIOLOGIC PROPERTIES OF MALIGNANT CELL SUBLINES AND CLONES OF A SPONTANEOUSLY METASTASIZING RAT MAMMARY ADENOCARCINOMA.

Neri A, Welch D, Kawaguchi T, Nicolson GL
(c/o Nicolson) Dept. Tumor Biology-108, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
JNCI; 68(3):507-517 1982

With the use of the rat 13762 mammary adenocarcinoma tumor, an animal model for spontaneous mammary tumor metastasis was developed. The parental tumor implanted sc into the mammary fat pads of female Fischer 344 rats metastasized at low frequency to lymph nodes and lung and did not metastasize to other organs. Oophorectomy did not modify the metastatic properties of the parental 13762 tumor. Cell lines were adapted to tissue culture from lymph node or lung metastases, and these were compared to parental tumor transplants in spontaneous metastasis assays. Only the cell lines established from metastases were spontaneously metastatic within 23 days after sc implantation, indicating that tumor cell populations from metastases are more metastatic than are cells from the parental tumor. Several individual parental tumor-derived and lung metastasis-derived clones were compared for spontaneous metastatic potentials, cell culture morphologies, histologic structures at primary implant and secondary metastatic sites, and growth characteristics in vivo and in vitro. There was no correlation between any of these tumor and cellular properties and metastatic potential. The parental mammary tumor-derived, lymph node metastasis-derived, and lung metastasis-derived cell lines and clones with differing spontaneous metastatic properties should prove useful in studies on the roles of tumor cell and host properties in lymphatic and blood-borne metastasis. (Author abstract) (57 Refs)

58. TEMPERATURE GRADIENTS AND LOCAL PERFUSION IN A MAMMARY CARCINOMA.

Gullino PM, Jain RK, Grantham FH
NCI, NIH, Bldg. 10, Room 5B-36, Bethesda, MD, 20205
JNCI; 68(3):519-533 1982

Temperature gradients of mammary tumors in random-bred Sprague-Dawley rats under normothermia, hypothermia, and hyperthermia were determined, and their experimental modifications were utilized to assess differences in perfusion rates within the neoplastic tissue. Normothermic tumors showed a circadian rhythm with zenith at midnight and nadir at midday. Differences between highest and lowest temperatures recorded during the 24-hr period reached up to 3 C. Similar oscillations were observed in sc tissue without tumor. An average temperature increment of 0.5-1.0 C was observed when a tumor was transferred from the sc to the abdominal location. Gradients larger than 1 C were observed within the same tumor in locations only a few millimeters distance from each other. The nonuniformity in temperature within normothermic tumors was exaggerated during hyperthermia. No appreciable change in temperature gradients was seen within a normothermic tumor when tumor blood flow was doubled or reduced to one-third of the basal level. Hyperthermia increased both volume and temperature of tumor efferent blood. As expected, decrease or increase in blood flow during hyperthermia increased or decreased tumor temperature, respectively, but substantial temperature gradients up to 2 C still persisted within adjacent regions. The extent of temperature changes in the tumor could not be correlated with a known change in blood supply. A pulse of cold serum into the tumor afferent artery produced a substantial reduction of tumor blood flow, but only a small depression in tumor temperatures, and a very small change in tumor temperature gradients. No appreciable modification could be brought about in tumor temperature levels and temperature gradients within the tumor by pulses of cold serum in the afferent artery during hyperthermia. After external cooling of the tumor, the time necessary to compensate for temperature depression did not correlate with either the reduction of temperature or with the thickness of the tumor tissue separating the thermistor from the cold source. The results indicate extensive anisotropy of temperature and blood distribution within growing neoplastic tissue and suggest that heat transfer by convection within the tumor is much less effective than it is commonly assumed. (Author abstract) (24 Refs)

59. ROLE OF NATURAL PROSTAGLANDINS IN THE CONTROL OF MURINE MAMMARY TUMOR VIRUS EXPRESSION.

Svec J, Svec P, Halcak L, Thurzo V

Cancer Res. Inst., Slovak Acad. Sciences, Csl. armady 21, CSSR-880 32 Bratislava, Czechoslovakia

J Cancer Res Clin Oncol; 103(1):55-67 1982

The regulation of murine mammary tumor virus (MuMTV) production by mammotropic hormones, hormonomimetic substances, and cyclic nucleotides was investigated. The virus produced in control and treated mammary tumor cell cultures was quantitated by measuring the supernatant reverse transcriptase activity in exogenous reaction using poly(rC).oligo(dG) as template-primer. Two days after exposure, the synthetic glucocorticoid, dexamethasone (DXMT), increased spontaneous MuMTV production at optimal concentration (0.1 umol) up to 10x. Dibutyryl derivative of cyclic AMP had no effect on spontaneous MuMTV production, whereas the drug potentiated suboptimal concentrations of the glucocorticoid. Natural prostaglandins, potent agonists of adenylate cyclase catalyzing intracellular synthesis of cyclic AMP, enhanced both basal (up to 5x) and DXMT-stimulated (up to 1.6 times) MuMTV replication. The MuMTV-stimulating activity of prostaglandins decreased in the order of PGA1 greater than PGE1 greater than PGB1 greater than PGF2 alpha. Prostaglandins can be replaced partially by norepinephrine and isoproterenol by enhancing the DXMT-mediated MuMTV stimulation, whereas these drugs remained without effect on spontaneous MuMTV production. Theophylline, an antagonist of cAMP-phosphodiesterase converting cAMP to AMP, enhanced the virus-stimulating activity of DXMT as well as of prostaglandins. The enhancement of MuMTV production by adenylate cyclase agonists do not correlate absolutely with the estimates of intracellular cAMP levels, since the highest amounts of cAMP have been repeatedly observed in cells treated with PGE1 and norepinephrine. The results indicate that besides hormones, other hormone-like substances and cyclic nucleotides may be involved in the complex mechanism of hormone-regulated MuMTV genome expression. (Author abstract) (55 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abel U 33
Abramowitz J 44
Alaghband-Zadeh 7
Alien J 7
Anderson KE 8
Austin FC 18
Bahi J 50
Bajetta E 34
Barclay TH 32
Barnes B 29
Barnes B 42
Barrett DL 3
Bartsch HH 21
Bause I 16
Becher R 33
Belhassen S 50
Belpomme D 30
Benjamin RS 29
Bertuzzi A 45
Biran S 46
Bishun NP 7
Black MM 32
Blank EW 17
Blossey HC 21
Blumenschein G 14
Blumenschein G 28
Blumenschein G 42
Blumenschein GR 29
Blumenschein GR 36
Blumenschein GR 37
Blumenschein GR 41
Blumenschien GR 26
Blumenshein GR 49
Bodey G 28
Bodey GP 26
Bodey GP 36
Bonadonna G 34
Boone CW 18
Borovik R 46
Borst JR 48
Boucher AE 27
Bower MA 6
Boyd NF 5
Bradlow HL 8
Brenner H 46
Brooks RJ 43
Brufman G 46
Bruntsch U 33
Burn JI 7
Buzdar A 14
Buzdar A 28
Buzdar A 29
Buzdar A 36
Buzdar A 41
Buzdar A 49
Buzdar AU 37
Canellos GP 39
Cantwell B 12
Carlile T 5
Case R 18
Cassidy J 38
Catalano RB 20
Cavins JA 18
Ceriani RL 17
Chase EM 43
Cheresh DA 56
Chew K 3
Clark J 4
Creech RH 20
Cumming JG 4
Cupissol D 19
Currie VE 23
Cuschieri A 4
D'Angelo T 47
Daidone MG 45
Davis SL 43
De Moss EV 47
Delgado M 30
DiStefano A 37
Distasio JA 56
Dixon R 27
Djerassi I 18
Dowsett M 25
Duguid H 4
Dykstra CJ 48
Eckles N 41
Edwards B 47
Egan EM 53
Ernster VL 3
Esparza L 24
Estes NC 11
Fabian CJ 55
Favier C 19
Favier F 19
Fennelly JJ 12
Fernandez D 7
Ferri HA 5
Fishell E 5
Fishman J 8
Forrest AP 51
Fracchia A 8
Frei E 39
Fritsche H 14
Fritze D 33
Frye D 42
Fumoleau P 30
Garnick MB 39
Gartside PS 2
Gary-Bobo F 19
Gary-Bobo J 19
Gazet JC 31
Gelman R 39
Giordano GF 43
Glover JL 11
Gorrell C 47
Grantham FH 58
Gregoire A 5
Guerrin J 30
Gullino PM 58
Hakes TB 23
Halcak L 59
Hankey BF 32
Harris AL 25
Harris AL 31
Harvey HA 27
Hawkins RA 51
Hayward JL 40
Helleberg A 1
Henderson IC 39
Hill S 36
Ho DH 41
Hoffmann F 52
Hopkins M 13
Hortobagyi G 14
Hortobagyi G 28
Hortobagyi G 29
Hortobagyi G 41
Hortobagyi G 42
Hortobagyi GN 24
Hortobagyi GN 36
Hortobagyi GN 49
Horwitz KB 6
Hutchinson F 4
Issell B 24
Jain RK 58
Jeffcoate S 25
Jones SE 43
Jungi WF 33
Kamaraju LS 50
Kanne D 21
Kantarjian H 41
Kaufman RJ 23
Kawaguchi T 57
Kehl A 16
Kelly PA 9
Kennedy BJ 10
Ketchel SJ 43
Kiang DT 10
Kiernan M 5
King EB 3
King RJ 40
Kinne D 23
Kinne D 8
Kirby R 55
Klein E 18
Kneba M 16
Koebberling J 21
Krieger G 16
Kufe DW 53
Kute TE 13
Legha S 28
Legha SS 36
Lessey BA 6
Levin DL 18
Levine PH 50
Lichter AS 47
Lippman ME 38
Lippman ME 47
Lipton A 27
Liu DK 54
Longley JD 5
Lopez DM 56
Lundgren B 1
Macgregor J 51
Majima H 22
Major PP 53
Malik R 36
Marchini S 34

Marie KS 20
Mathe G 30
Mayer RJ 39
Mayr A 33
McKinna JA 31
Mehta RG 13
Meltzer N 55
Metz R 30
Miller AB 5
Miller D 11
Misset JL 30
Mockus MB 6
Montague ED 49
Moon RC 13
Moon TE 43
Moorhead EL 48
Morgan MW 31
Moskowitz M 2
Moskowitz M 5
Mourali N 50
Muenz LR 50
Mughal A 14
Murray TV 48
Nagel GA 16
Nagel GA 21
Neill G 4
Neri A 57
Nguyen M 19
Nicolson GL 57
Nixon SJ 51
Oettgen H 23
Parker LM 39
Pawl LR 48
Peterson JA 17
Petitclerc M 5
Petrakis NL 3
Pierce V 8
Pinnamaneni K 37
Pinsky C 23
Plagne R 30
Potchen M 48
Powell KC 49
Preece PE 4
Pujol H 19
Queisser W 33
Ragaz J 15
Rath P 46
Robinson E 46
Rosner D 18
Rosner D 35
Rubens RD 40
Ryan C 12
Salinas FA 15
Salmon SE 43
Sun Diego E 48
Santen RJ 27
Sargent L 53
Sasaki M 17
Schell F 29
Schell F 42
Schell FC 24
Schell FC 26
Schneider J 8
Senn HJ 33
Serrou B 19
Shafik AS 27
Shah MK 20
Silver HK 15
Silvestrini R 45
Simor IS 5
Skarin AT 39
Smethurst M 7
Smith IE 25
Smith IE 31
Snover D 10
Steele R 51
Steiner R 40
Stephens RL 55
Sternson L 55
Stewart JF 40
Stierlin H 52
Svec J 59
Svec P 59
Swanson D 14
Tabbane F 50
Tancini G 34
Thurzo V 59
Tilzer L 55
Turcot-Lemay L 9
Valagussa P 34
Veronesi U 34
Vogel CL 56
Watanabe A 11
Weber G 52
Wee KH 15
Welch D 57
Wesley M 38
White DS 27
Williams DC 7
Wirsching B 52
Wirsching M 52
Wisbey ML 4
Wolfson C 5
Wood RA 4
Yap H 14
Yap H 28
Yap H 41
Yap HY 24
Yap HY 26
Yap HY 29
Yap HY 36
Yap HY 49
Yap Y 42
YapHY 37
Young RC 38
Zhang HJ 10

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS).......... 1-2
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS.......... 3-7
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS.......... 8-11
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS.......... 12-14
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY).......... 15-20
- SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY.......... 21
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY).......... 22-23

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. SCREENING, DETECTION, AND DIAGNOSIS OF BREAST CANCER.

Miller AB, Bulbrook RD
Epidemiology Unit, Natl. Cancer Inst. Canada, Univ. Toronto, Toronto, Ontario M5S 1A8, Canada
Lancet; 1(8281):1109-1111 1982

Principles of breast cancer (BC) screening, methodology to evaluate screening programs, detection methods for BC, problems raised by the detection of small invasive and in situ BC, and results of BC screening are reviewed. Risk factors and selection for screening, periodicity of re-screening, and cost-effectiveness also are discussed. Screening and diagnosis are compared. The ideal methodology for the evaluation of screening programs is the randomized controlled trial. Detection methods for breast cancer include self-examination, mammography, and thermography. Lesions encountered in large numbers in screening programs include benign atypical hyperplastic lesions, borderline abnormalities which may be difficult to distinguish from in situ carcinomas, in situ ductal and lobular car-

HE 20.3173/2:

cinomas, and small invasive carcinomas. Optimal management of in situ lesions is considered. Results of BC screening programs indicate the value of screening asymptomatic women aged 50 yr and older by the combination of mammography and physical examination of the breast. (no Refs)

2. CLINICAL EXAMINATION AS A SCREENING METHOD FOR BREAST CANCER.

McLatchie G, McArdle C, Menzies T
Southern General Hosp., Glasgow, Scotland
Scott Med J; 27(2):152-153 1982

A five-year experience of a breast cancer screening clinic in a Scottish urban area is reported. During this period 28% of the female population aged 25 to 70 yr was screened by clinical examination alone. The pick-up rate for cancers was 7.8 per 1,000 'well' women examined, and 21% of all patients with cancer were under 40 yr old. Clinical examination is an effective and economical method of screening for breast cancer. The establishment of similar clinics to detect breast disease in women of all age groups is recommended. (Author abstract) (4 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

3. SO-CALLED INTERVAL CANCERS OF THE BREAST PATHOLOGIC AND RADIOLOGIC ANALYSIS OF SIXTY-FOUR CASES.

Holland R, Mravunac M, Hendriks JH, Bekker BV
Dept. Pathology, Univ. Nijmegen, Geert Grooteplein Zuid 24, 6525 GA Nijmegen, The Netherlands
Cancer; 49(12):2527-2533 1982

Within a population-based breast cancer screening program, 209 cancers were detected by regular mammographic screening. Additionally, 66 cancers were discovered between two consecutive screenings after one, two, or three negative screening examinations (interval cancers). The study group consisted of 25,920 women who have been participating since 1975 in a breast cancer screening program in Nijmegen, The Netherlands. In this program, single view mammography (lateromedial projection) was administered as the sole screening examination every 2 yr. Physical examination was not part of the screening program. All previous histologic and radiologic material from 64 of those 'interval' patients was available and was reviewed. In 19 of the 64 patients, direct or indirect signs of tumor were seen on the previous screening mammogram on review (observers error). In four cases, the site of the tumor lay outside the imaging field (technical error). In 41 cases, no signs of tumor could be seen on the mammograms even on review. By calculated tumor doubling times, 20 of these 41 cases were probably too small to be detected at the last screening ('real' interval cancers). However, 21 cases were probably large enough but were somehow masked from radiologic detection. The main reasons for this 'masking' proved to be: (1) dense breast, (2) poorly outlined tumor mass of diffuse infiltrative type, mainly invasive lobular carcinomas, and (3) intraductal localization. The authors suggest that women with dense breasts be screened more frequently, using more views and modalities and with broader criteria for advising surgical biopsy. They also note that in general the 2-yr interval between screenings is probably longer than the optimal interval. (Author abstract) (10 Refs)

4. THE DIAGNOSIS OF BENIGN DISEASE AND THE EXCLUSION OF MALIGNANCY IN PATIENTS WITH BREAST SYMPTOMS.

Croll J, Kotevich J, Tabrett M
Sydney Square Diagnostic Clinic, 2nd Floor, St. Andrew's House, Sydney Square 2000, Australia
Semin Ultrasound; 3(1):36-50 1982

Pilot study of 1,500 symptomatic patients to test methodology and data collection and findings and results of follow-up of 4,850 patients are discussed. Women under 25 yr old were examined by double-blind surgical opinion (DBSO) and by ultrasonography. Women over 25 yr old were examined by DBSO and routine film-screen and/or xeromammography. Performance of ultrasound mammography and interpretation of sonograms including skin line and nature of a mass are discussed. Benign conditions which are well demonstrated ultrasonically are unilateral breast development, unilateral hyperthrophy, benign tumors causing gross unilateral breast enlargement, unusual conditions in prepubertal girls, benign mammary dysplasia, duct ectasia, breast abscess, fat necrosis, hematoma, examination during pregnancy and lactation, augmentation mammoplasty, gross cystic disease, fibroadenoma, cystosarcoma phylloides, mixed benign pathology, and mixed benign and malignant pathology. Being lesions which present diagnostic difficulties ultrasonically are cysts with internal echoes or without posterior enhancement, localized areas of active dysplasia, inflammatory disease, and circumscribed carcinoma. In a series of 173 cancers, mammography correctly called 88% malignant and 3% suspicious of malignancy, a total of 91%, giving a false negative rate of 9%. Sonography in the same patients was malignant in 81% and suspicious in 4%, giving a false negative rate of 15%. The false negative rate for surgical opinion in the same patients was 10%. Ultrasonography correctly classified 99% of discrete clinical or mammographic masses into cystic or solid. (4 Refs)

5. PROGNOSTIC INDICATORS IN BREAST CANCER - MORPHOMETRIC METHODS.

Baak JP, Kurver PH, De Snoos-Niewlaat AJ, De Graef S, Makkink B, Boon ME
Dept. Pathology, Stichting Samenwerking, Delftse Ziekenhuizen, Reiner de Graefweg 7, Delft, The Netherlands
Histopathology; 6(3):327-339 1982

Tumor diameter, mitotic activity, cellularity index, and quantitative microscopic nuclear features were determined using histological material from 78 breast cancer patients (av 53.4 yr old) who either died from the cancer within a 6.5 yr follow-up period (42 nonsurvivors) or lived for a longer time without evident metastases (36 survivors). Many significant differences between survivors and nonsurvivors were observed in objective and subjective parameters. The tumors of the survivors were smaller, had a slightly higher cellularity index, a lower mitotic index, and smaller nuclei. The standard deviations of all nuclear features were smaller in the survivors, indicating less nuclear pleomorphism. In the survivors the nuclear grade was higher and the histological grade lower. Using tumor diameter and quantitative microscopical features, most survivors could be distinguished from nonsurvivors. The percentage of 'doubtful' classifications is much higher with the TNM and subjective grading methods than with morphometry. Axillary lymph node status and tumor diameter can be used to predict prognosis in breast cancer with an accuracy of approx 60%, but use of objective quantitative parameters yields a significantly higher prognostic accuracy (82%). (33 Refs)

6. INTERNAL MAMMARY LYMPHOSCINTIGRAPHY IN BREAST CARCINOMA: POSSIBLE SIGNIFICANCE IN RELATION TO CURRENT TREATMENT.

Manji MF
Cancer Control Agency British Columbia, 2656 Heather St., Vancouver, B.C., V5Z 5J3, Canada
J Can Assoc Radiol; 33(1):10-14 1982

A diagnostic modality to study parasternal lymph nodes was examined at the Cancer Control Agency of British Columbia, Vancouver. Forty-five patients with carcinoma of the breast were studied. The data correlate well with that from other centers in regard to anatomic validity, lymph node distribution, cross drainage and findings in relation to the stage of disease. The frequency of lymphoscintigraphic abnormalities was almost twice as high in relation to lesions situated in the center and inner half of the breast as compared with outer half lesions. Twenty-eight percent of patients demonstrated cross drainage between parasternal lymphatics. In 11% of the patients, nodes were situated at locations greater than 4 cm from the midline. Work is in progress to study the correlation of lymphoscintigraphy with disease in the nodes. The data indicate that this study can be used in other centers in the management of patients with mammary carcinoma. (Author abstract) (16 Refs)

7. ANGIOSARCOMA OF THE BREAST: A PATHOLOGIC STUDY OF FORTY PATIENTS (MEETING ABSTRACT)

Donnell R, Rosen PP, Lieberman PH, Kay S, Kaufman R, Braun D
Vanderbilt University, Nashville, TN
Lab Invest; 46(1):19A 1982

Angiosarcoma of the breast is a rare malignant tumor that has generally been considered as almost uniformly fatal. No one group of pathologists has previously reviewed and reported a significant number of cases, and the spectrum of morphology has not previously been analyzed. We undertook this study to more clearly define the pathologic features of these tumors, to see whether the microscopic features can be related to prognosis, and to try to identify a group of patients who might benefit from adjuvant chemotherapy. We reviewed the clinical and pathologic features of 40 cases of angiosarcoma seen at Memorial Hospital and at the Medical College of Virginia in the past 40 years. Histologic sections were studied without knowledge of the clinical course or follow-up, and each case was placed into one of three groups on the basis of microscopic features to be described. Treatment and follow-up data were obtained from various sources. We found that the histologic appearance of angiosarcomas of breast is a good prognostic indicator. Whereas 10 of 13 patients in histologic group I were alive and free of disease with an average follow-up of nearly 6 years, only two of 16 group III patients were free of disease, and 14 have died with metastatic disease. The group II patients had a survival similar to those in group I. In this series the disease-free survival at 3 years was 41 per cent and at 5 years 33 per cent, much better then that reported in previous reviews of mammary angiosarcoma. (no Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

8. A MICRO-ASSAY FOR ESTROGEN RECEPTOR IN BREAST TUMOR WITH USE OF 125I-LABELED ESTRADIOL.

Van NT, Fritache HA, Trujillo JM
Dept. Lab. Medicine, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77036
Clin Chem; 28(6):1303-1308 1982

The concentration of estrogen receptor protein in breast-tumor tissue is generally expressed in units of femtomoles of estradiol bound by the receptor per milligram of cytosol protein. The sensitivity of the estrogen receptor radioligand assay is therefore related to the specific activity of the steroid label used for the binding assay, the amount of the receptor protein in the vol of cytosol used, and the protein concentration in the cytosol. In this paper, we discuss factors affecting the sensitivity of the estrogen receptor assay and present various approaches for optimizing the assay. We also describe a procedure that involves a radioiodinated estradiol of high specific activity, a micro-technique for preparing tumor cytosol, and a micro-assay procedure with which the estrogen receptor protein can be measured in as little as 50 mg (wet weight) of tissue. (Author abstract) (7 Refs)

9. MULTIPLE SIMULTANEOUS AND SEQUENTIAL ESTROGEN RECEPTOR VALUES IN PATIENTS WITH BREAST CANCER.

Peetz ME, Nunley DL, Moseley HS, Keenan EJ, Daveport CE, Fletcher WS
(c/o Fletcher) Dept. Surgery, Div. Surgical Oncology, Oregon Health Sciences Univ., 3181 S.W. Sam Jackson Park Road, Portland, OR, 97201
Am J Surg; 143(5):591-594 1982

Fifty-nine women had multiple estrogen receptor assays done, either simultaneously or sequentially. Eight-six percent of the patients who had multiple synchronous estrogen receptor assays from various metastatic sites showed no significant discrepancy in estrogen receptor values. When estrogen receptor assays were done sequentially without intervening therapy, 83.5% of the patients maintained their initial positivity or negativity. However, when the second estrogen receptor determination was preceded by either chemotherapy or hormonal therapy, 33% of the patients had a significant discrepancy in estrogen receptor values. The most common discrepancy was estrogen receptor-positive tumors becoming estrogen receptor-negative, although a small number of patients were found whose receptor values became more positive after hormonal ablation. (Author abstract) (18 Refs)

10. ESTROGEN RECEPTOR HETEROGENEITY AND THE RELATIONSHIP BETWEEN ESTROGEN RECEPTOR AND THE TRITIATED THYMIDINE LABELING INDEX IN HUMAN BREAST CANCER.

Straus MJ, Moran R, Muller RE, Wotiz HH
Div. Neoplastic Diseases, New York Medical Coll., Valhalla, NY, 10595
Oncology; 39(4):197-200 1982

Tissue from 54 patients with breast cancer was analyzed for estrogen receptor (ER). From 38 patients, tissue from multiple tumor sites was analyzed to determine ER heterogeneity. In 13 patients (34%) both positive and negative ER values were obtained. ER negative (ER-) results were observed more frequently in metastatic lesions. In 28 patients both the ER and [3H]-thymidine labeling index (LI) were measured in the same lesion. [3H]-Thymidine was administered in vivo. There was a positive correlation between ER positivity and low LI. The mean LI of 8 ER positive (ER+) tumors was 3.4 in contrast to a mean LI of 10.0 for 14 ER-tumors (p less than 0.01). LI of 6 mixed ER tumors (E+/-) was intermediate (mean 5.7). High LI (greater than or equal to 8) was associated with decreased survival regardless of the stage of disease at the time of study. ER with LI may provide an improved basis for treatment selection. (Author abstract) (17 Refs)

11. PROGNOSTIC VALUE OF CYCLIC AMP BINDING PROTEIN IN HUMAN BREAST CANCER (MEETING ABSTRACT)

Senbanjo RO, Miller WR, Telford J, Watson D, Forrest AP
Department of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Cyclic adenosine -3'5' - Monophosphate (cyclic AMP) and its binding proteins are involved in regulating the growth of mammary tumors in experimental animals. In the present study, we have investigated the relationship between cyclic AMP binding proteins in human breast cancers and clinical parameters including prognosis. The binding proteins were measured in the cytosols from 75 human breast cancers. All tumors contained measurable binding proteins, levels varying from 0.81 to 15.05 omols/mg cytosol protein. No relationship was found between level of activity and menopausal status of the patient, clinical stage of the disease, presence or absence of nodal involvement or histological grade of the tumor. A group of 11 patients who at the time of primary treatment had no evidence of metastatic disease but have developed recurrence within 36 months have been compared with a similar group (10 patients) who have had a minimum of 20 months follow-up and were disease-free. Levels of cyclic AMP binding proteins was significantly higher in tumors from women having early recurrence than in those who were disease-free. The range in disease-free patients was 1.57-7.21 omols/mg cytosol protein; whereas that in 10 of 11 tumors with subsequently recurred early was 7.75-13.02. (2 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

12. LYMPHOCYTE SUBSETS INFILTRATING HUMAN MAMMARY CARCINOMAS (MEETING ABSTRACT)

Eremin O, Ashley J, Brown M, Williamson S
Department of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Lymphocytes infiltrating human mammary carcinomas have been well documented histologically but their precise role in vivo and possible anti-tumor activity has not been defined. Lymphocytes were isolated from primary human mammary tumor using mechanical and enzymatic preparative techniques and cell passage down a sephadex G-10 column. Rosetting techniques were used to characterize both T and B lymphocyte subsets within the tumors. The pattern detected was different, in certain respects, from that found in the blood and suggested a selective subset migration into the tumor. This was confirmed by in vitro cytotoxicity assays revealing an absence of K cells and a paucity of NK cells. The study also established the hyporeactive state (mitogen assays) of the tumor-infiltrating lymphocytes, in contrast to the normal activity of blood lymphocytes. (no Refs)

13. IMMUNOPEROXIDASE LOCALIZATION OF LACTALBUMIN IN MALIGNANT BREAST NEOPLASMS.

Clayton F, Ordonez NG, Hanssen GM, Hanssen H
(c/o Ordonez) Dept. Pathology, Texas Medical Center, Univ. Texas, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Arch Pathol Lab Med; 106(6):268-270 1982

By an immunoperoxidase method, lactalbumin was demonstrated in the cytoplasm of epithelial cells of normal breast, primary and metastatic breast carcinomas, and benign breast disease. Lactalbumin was present in 39 of 64 breast carcinomas of different types, including 77% (31) of infiltrating ductal carcinomas and 42% (7) of infiltrating lobular carcinomas. It also was present in 55% (nine) of metastatic breast carcinomas and in 100% (5) of fibroadenomas. Lactalbumin was not observed in normal tissues and malignant neoplasms of other tissues, indicating that lactalbumin can serve as a specific tissue marker for malignant neoplasms of the breast and their metastases. (Author abstract) (16 Refs)

14. CARCINOEMBRYONIC ANTIGEN AND ALPHA-LACTALBUMIN IN BREAST CARCINOMA: AN IMMUNOHISTOCHEMICAL STUDY (MEETING ABSTRACT)

Kuhajda FP, Mendelsohn G
Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD
Lab Invest; 46(1):46A 1982

Carcinoembryonic antigen (CEA) is a valuable marker in many carcinomas, whereas alpha-lactalbumin (ALA), a protein produced by breast epithelial cells, is specific for breast carcinoma. Conflicting reports exist concerning CEA and ALA in different histologic types of breast carcinoma. To evaluate the distribution and staining characteristics of these markers, we stained 62 assorted in situ and infiltrating breast carcinomas, numerous benign breast lesions, and normal breast tissue using the immunoperoxidase technique. Positive immunostaining for CEA was observed in 62 per cent of carcinomas, but not in normal breast or benign breast lesions including papillomas and duct papillomatosis. ALA was present in 76 per cent of carcinomas and focally positive in normal breast epithelium and in four papillomas. In situ lobular carcinoma stained poorly for both CEA and ALA; ALA was present in 77 per cent of infiltrating lobular carcinomas, whereas CEA was present in only 32 per cent. There was no significant difference in CEA and ALA staining in lymph node metastases from 14 patients. However, lymph node metastases were more frequent in cases of infiltrating duct carcinoma with strong CEA positivity. (no Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

15. PHASE II STUDY OF AMSA IN PATIENTS WITH METASTATIC BREAST CANCER: A CANCER AND LEUKEMIA GROUP B STUDY.

Amrein PC, Coleman M, Richards F, Poulin RF, Bernhardt B, Ginsberg SJ, Green MR, Morrison A, Cortes E, Kiang D, Weinberg V, Wood WC
Hematology-Oncology Unit, Cox 6, Massachusetts General Hosp., 100 Blossom St., Boston, MA, 02114
Cancer Treat Rep; 66(5):1211-1213 1982

A phase II study of 4'-(9-acridinylamino)methanesulfon-m-anisidide (AMSA) in 77 patients (av age, 56; range 28-74 yr old) with measurable, metastatic breast cancer is described. AMSA was initially administered at a dose of 60 or 120 mg/square meter (m2), depending on the extent of prior chemotherapy and radiotherapy. Treatments were given every 3 wk and doses were increased by 20 mg/m2 with each treatment until toxicity was encountered or a level of 160 mg/m2 was achieved. Seventy-six patients were evaluable for toxicity. The dose-limiting toxic effect was myelosuppression; WBC counts were more sensitive than platelet counts. Overall, 17% had WBC count nadirs between 1,000 and 2,000/ul, while 14% had WBC counts less than 1,000/ul. Thrombocytopenia was less severe; only 10% had a platelet count less than 50,000/ul, and no bleeding problems were encountered. Approx 22% of patients experienced some nausea or vomiting and 4% developed stomatitis. Of the 77 patients evaluable for response, 3 showed partial remission (PR) and 3 showed improvement short of PR. Sites of measurable disease response were in skin, nodes, and lung. Durations of PR were 4, 5, and 15 wk. Two PR occurred at a starting does of 70 mg/,2, while one occurred at a starting dose of 120 mg/m2. (6 Refs)

16. THE SITE OF ACTION OF AMINOGLUTETHIMIDE (AG) IN ADVANCED BREAST CANCER (MEETING ABSTRACT)

Harris AL, Dowsett M, Jeffcoate S, Smith IE
Royal Marsden Hospital, Fulham Road, London, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Short Synacthen tests (250 ug Synacthen IM) were performed on 10 post-menopausal women with advanced breast cancer who had received AG 250mg 4 x day plus hydrocortisone 20mg 2 x day for at least 3 months. There was no significant rise in cortisol, estrone or dehydroepiandrosterone sulphate. However, 17OH progesterone (17OHP), delta 4 androstenedlone (delta 4A) and dehydroepiandrosterone rose markedly. 17OPH rose by up to 53 fold, and delta 4A up to 10.8 fold. This pattern of response to ACTH suggests that there is little inhibition of desmolase by AG, but that inhibition of aromatase is more important and even a marked rise in precursors does not overide aromatase inhibition. Since conventional dose AG is given to inhibit desmolase we used low dose AG without hydrocortisone to inhibit aromatase, which in vitro is more sensitive than desmolase. Twelve postmenopausal patients were given AG 125mg 2 x day for 1 week and in all patients estrone fell (50% of baseline). AG was then doubled each week until 500 mg 2 x day. Estrone at the highest dose of AG was 54 of baseline. The addition of 20mg hydrocortisone 2 x day did not further suppress estrone (55% of baseline). This suggests that adrenal suppression by hydrocortisone does not contribute to the effect of AG and that low dose AG alone should be assessed for therapeutic effect. (no Refs)

17. TREATMENT WITH A LUTEINISING-HORMONE-RELEASING-HORMONE ANALOGUE (BUSERELIN) IN PREMENOPAUSAL PATIENTS WITH METASTATIC BREAST CANCER.

Klijn JG, DeJong FH
Dr. Daniel den Hoed Kliniek, Rotterdamsch Radio-Therapeutisch Instituut, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands
Lancet; 1(8283):1213-1216 1982

Four premenopausal women with metastatic breast cancer were treated with a potent luteinizing-hormone-releasing-hormone (LHRH) analogue as a single first-line agent. Buserelin (6-D-ser-(bu1)-LHRH-(1-9)-ethylamide) was given in very high doses intravenously and then intranasally; ovarian function did not decrease within 1-2 wk, but after this period low to very low (postmenopausal) plasma estradiol levels were reached in all patients, accompanied by flushes. Two patients, however, subsequently showed transient peaks of plasma estradiol, probably due to a persistent follicle, which lasted for some wk without a rise in plasma luteinizing hormone, follicle-stimulating hormone, or progesterone. In two patients there was no significant change in the tumor, whereas in the other two patients there was remarkable improvement. (Author abstract) (22 Refs)

18. POLY A-POLY U, A NEW ADJUVANT TREATMENT IN OPERABLE BREAST CANCER.

Lacour F, Lacour J, Spira A, Michelson M, Delage G, Petit JY, Contesso G, Merlin-Nahon E, Sarrazin D, Michel G, Viguier J
Institut Gustave-Roussy, rue Camille-Desmoullins, F 94800 Villejuif, France
Gynecologie; 32(6):527-531 1981

Three hundred women with operable infiltrating adenocarcinomas of the breast (mean size of 2-7 cm) underwent conventional treatment (CT: mastectomy plus lymphatic or internal breast curettage) with (155 patients) or without (145: controls) adjuvant poly A-poly U (PAPU: 30 mg iv, weekly for 6 wk) administration. The CT and CT + PAPU groups were comparable with regard to principal clinical, histological, and prognostic factors, treatment, and hormonal status. Cancer mortality for the CT group was elevated (36/145 patients) as compared with the CT + PAPU group (21/155). Metastases were observed in 43/145 CT patients and in 32/155 CT + PAPU patients. The 5-yr survival rates for the CT and CT + PAPU groups were 47% and 71%, respectively. Advantages of adjuvant PAPU use in the treatment of operable breast tumors are discussed. (16 Refs) (In FRE)

19. MARROW NEUTROPHIL RESERVE AFTER ADJUVANT CHEMOTHERAPY FOR CARCINOMA OF THE BREAST.

Corder MP, Jochimsen PR
Dept. Internal Medicine, Preventive Medicine, Univ. Iowa Hosp., Iowa City, IA, 52242
Cancer; 49(12):2455-2458 1982

The hematologic factors of 16 female patients with breast carcinoma who had received adjuvant chemotherapy with L-phenylalanine-based programs for 2 yr were compared with those for 13 normal female volunteers of similar age. The findings include significant suppression of the mean hemoglobin level, of leukocyte counts, and of circulating neutrophils and lymphocytes in patients 3-27 mo after chemotherapy. Marrow neutrophil reserve studies with prednisolone stimulation again demonstrated significant suppression for the patients who had received chemotherapy. The authors conclude that there is a chronic hematologic toxicity associated with this therapy. (Author abstract) (28 Refs)

20. A CASE OF BREAST CARCINOMA IN A 24-YR-OLD MALE.

Bacci M, Cavallere A, Fama G
Inst. Pathological Anatomy and Histology, Perugia Univ., Perugia, Italy
Pathologica; 74(1029):117-121 1982

Gynecomastia was diagnosed and a firm, painless tumor adherent to the base of the breast beneath the nipple was surgically removed from a 24-yr-old man. Macroscopically, the neoplasm was a greyish-white, fleshy, roundish mass 3 cm in diameter. Histological examination of surgical specimen revealed an infiltrating ductal carcinoma with adenocarcinomatous features. A radical mastectomy was performed and axillary lymph nodes removed. Adjacent breast tissue showed hyperplasia. Diffuse histiocytosis was found in all lymph nodes examined. Etiological, pathogenic, and prognostic features of male breast carcinoma are discussed. (19 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

21. RISK FACTORS FOR BREAST CANCER IN WOMEN IN NORTHERN ALBERTA, CANADA, AS RELATED TO AGE AT DIAGNOSIS.

Lubin JH, Burns PE, Blot WJ, Lees AW, May C, Morris LE, Fraumeni JF
Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 68(2):211-217 1982

A population-based case-control study involving interviews with 577 female breast cancer patients and 826 controls in northern Alberta, Canada, revealed that some determinants of breast cancer varied according to age. Among women under age 45, risk factors included a younger age at menarche, late age at last birth, high parity, and recent use of oral contraceptives. At older ages risk was related to natural as opposed to surgical menopause, late age at first birth, low parity, late age at natural menopause, and tonsillectomy. At all ages there was an increased risk of breast cancer associated with difficulty in conceiving, benign breast disease, not having breast fed, and a history of breast cancer among mothers or sisters. For some variables the age differences were pronounced; the combination of low parity and late age at first birth was associated with a sevenfold increase in breast cancer risk at ages 55-80 but a slight decrease at ages under 45. The effect of tonsillectomy steadily increased with age and represents a new lead, but certain features of the data suggest that the link to oral contraceptives among younger women and the inverse relation to breast feeding at all ages may not be causal. Even though design limitations (cases interviewed in a different setting from controls) appeared not to influence conclusions, the results may have been subjected to interview bias and thus should be interpreted cautiously. (Author abstract) (26 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

22. INFLUENCE OF DELAYED ADMINISTRATION OF RETINYL ACETATE ON MAMMARY CARCINOGENESIS.

McCormick DL, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Cancer Res; 42(7):2639-2643 1982

Administration of a dietary retinoid supplement beginning 1 wk after carcinogen administration is highly effective in the inhibition of rat mammary carcinogenesis. A study was designed at two carcinogen dose levels to determine to what extent retinoid feeding can be delayed and retain its chemoprotective effect. In the high-dose experiments, groups of 30 virgin female Sprague-Dawley rats received a single iv dose of 50 mg N-methyl-N-nitrosourea (MNU) per kg body wt and were fed a dietary supplement of 328 mg retinyl acetate per kg diet beginning at 1, 4, or 8 wk after MNU administration. In the low-dose experiment, groups of 50 rats received 25 mg MNU per kg, and the retinoid was begun at 1, 4, 8, 12, 16, or 20 wk post-MNU. Controls at both dose levels received a placebo diet beginning 1 wk after carcinogen treatment. At the high MNU dose, retinyl acetate was most effective in inhibition of carcinogenesis when treatment was begun 1 wk after MNU administration. Delaying retinyl acetate feeding until 4 wk post-MNU resulted in slightly reduced chemoprotective efficacy, while an 8-wk delay caused a complete loss of anticancer activity. At the low MNU dose, delaying retinyl acetate administration for up to 12 wk after MNU administration caused no loss of chemopreventive efficacy. A 16-wk delay resulted in decreased anticancer activity, while retinoid treatment begun 20 wk post-MNU had no effect on cancer induction. Retinoid administration can be delayed beyond 1 wk and retain its activity against rat mammary carcinogenesis; the length of delay allowable without loss of activity is a function of tumor latency. (Author abstract) (15 Refs)

23. RECEPTOR BINDING AND PROCESSING OF EPIDERMAL GROWTH FACTOR BY HUMAN BREAST CANCER CELLS.

Osborne CK, Hamilton B, Nover M
Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284
J Clin Endocrinol Metab; 55(1):86-93 1982

Epidermal growth factor (EGF) stimulates the growth of human breast cancer cells (MCF-7). To better define the mechanisms for these effects, we studied receptor binding and subsequent processing of [125I]EGF in cells growing in monolayer culture under conditions in which an effect on growth is observed. Binding was temperature dependent and was higher at reduced temperature. At 37 C, binding rapidly reached a maximum (20-60 min) and then gradually decreased. Binding was slower at a reduced temperature. High affinity was demonstrated by the ability of unlabeled EGF to compete for [125I]EGF binding; half maximal displacement was observed at an EGF concentration that also resulted in half-maximal biological activity (1-2 ng/ml). Scatchard plots derived from these data or from those of studies using increasing concentrations of [125I]EGF were curvilinear and superimposable. Plots from binding data obtained at 0 C were also curvilinear, suggesting that the processing and degradation of tracer alone cannot explain this finding. Other peptides did not compete for EGF binding. During a 6-hr incubation, progressive degradation of [125I]EGF occurred on and/or in the cells, with prompt release of low mol wt fragments into the medium. Furthermore, during this time, the bound intact EGF became more resistant to dissociation by excess unlabeled EGF. Reduced binding (50%), not due to simple occupancy, was also noted during a 2-hr preincubation with unlabeled EGF, indicating down-regulation of receptor. These data suggest the following sequence of events. At 37 C, EGF rapidly binds to specific receptors on MCF-7 cells. The bound EGF becomes more and more difficult to dissociate from the cell, and the number of available receptors is reduced, implying sequestration in the cell membrane and/or internalization of the hormone-receptor complex. Gradually, EGF is degraded, and the products are released from the cell. Human breast cancer appears to be a target for EGF action. (Author abstract) (24 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Amrein PC 15
Ashley J 12
Baak JP 5
Bacci M 20
Bekker BV 3
Bernhardt B 15
Blot WJ 21
Boon ME 5
Braun D 7
Brown M 12
Bulbrook RD 1
Burns PE 21
Cavaliere A 20
Clayton F 13
Coleman M 15
Contesso G 18
Corder MP 19
Cortes E 15
Croll J 4
Daveport CE 9
De Graef S 5
De Snoos-Niewla 5
DeJong FH 17
Delage G 18
Donnell R 7
Dowsett M 16
Eremin O 12
Fama G 20
Fletcher WS 9
Forrest AP 11
Fraumeni JF 21
Fritsche HA 8
Ginsberg SJ 15
Green MR 15
Hamilton B 23
Hanssen GM 13
Hanssen H 13
Harris AL 16
Hendriks JH 3
Holland R 3
Jeffcoate S 16
Jochimsen PR 19
Kaufman R 7
Kay S 7
Keenan EJ 9
Kiang D 15
Klijn JG 17
Kotevich J 4
Kuhajda FP 14
Kurver PH 5
Lacour F 18
Lacour J 18
Lees AW 21
Lieberman PH 7
Lubin JH 21
Makkink B 5
Manji MF 6
May C 21
McArdle C 2
McCormick DL 22
McLatchie G 2
Mendelsohn G 14
Menzies T 2
Merlin-Nahon E 18
Michel G 18
Michelson M 18
Miller AB 1
Miller WR 11
Moon RC 22
Moran R 10
Morris LE 21
Morrison A 15
Moseley HS 9
Mravunac M 3
Muller RE 10
Nover M 23
Nunley DL 9
Ordonez NG 13
Osborne CK 23
Peetz ME 9
Petit JY 18
Poulin RF 15
Richards F 15
Rosen PP 7
Sarrazin D 18
Senbanjo RO 11
Smith IE 16
Spira A 18
Straus MJ 10
Tabrett M 4
Telford J 11
Trujillo JM 8
Van NT 8
Viguier J 18
Watson D 11
Weinberg V 15
Williamson S 12
Wood WC 15
Wotiz HH 10

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BREAST CANCER

Diagnosis, Treatment, Pre-Clinical Biology

SERIES CT09 No. 82/11

NOVEMBER, 1982

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In this issue:

- **BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)** 1
- **DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS** 2-12
- **BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS** 13-17
- **CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS** 18-20
- **BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)** 21-37
- **SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY** 38
- **SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)** 39-43

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. THE PLACE AND METHODS OF BREAST SCREENING.

Sacharias N
Dept. Radiological Sciences, Alfred Hosp., Melbourne, Australia
Australas Radiol; 26(1):17-24 1982

Breast screening through the use of clinical examination (CE), thermography (TG), mammography (MG), computed tomography (CT), and ultrasound (US) is discussed. Of palpable breast cancers (BC), 7-10% cannot be detected using MG and TG. However, CE is not effective in detecting sub-clinical and minimal BC. TG is relatively non-specific and and poorly localizes tumor site but can be an indicator of early BC. MG is the chief method of nonclinical breast screening. Most small BC are detected by MG alone. The accuracy and specificity of MG findings varies according to the type of lesion. CT can examine the av breast with 5-6 sections giving a mid breast dose of 0.175 rads/6 sections. It has been suggested that CT can accurately distinguish between benign and malignant lesions based on differences in attenuation values after contrast infu-

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sion. Conventional gray scale echography is an extremely useful adjunct in a screening situation to distinguish between solid and cystic lesions and examining dense masses for components of varying tissue type. The water bath technic of US is discussed. Determination of a population to be screened is considered. It was suggested that MG, complemented by CE and US, is a good screening test for BC. (40 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. A CONTRIBUTION TO THE NATURAL HISTORY OF BREAST CANCER. I. DUCT OBLITERATION WITH PERIDUCTAL ELASTOSIS IN THE CENTRE OF BREAST CANCERS.

Egger H, Dressler W
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany
Arch Gynecol; 231(3):191-198 1982

Serial sections of 100 breast carcinomas of 20 mm max diameter were made, stained with several stains simultaneously, and examined for periductal elastosis and obliterated ducts. The median age of patients was 56.2 yr (range 31-83 yr), with two peaks: one between 50 and 55 and another between 60 and 65. Body weight, parity, menopause, and frequency of diabetes and no apparent relation to the frequency of mammary duct obliteration and periductal elastosis at the center of the carcinoma. The frequency of duct obliteration with periductal elastosis exhibited two peaks, each of which preceded by about 10 yr the incidence peaks for mammary carcinoma in the patient population. Carcinomas with duct obliteration and periductal elastosis were more frequently easily palpable (90%) than tumors without this phenomenon (50%), and had other distinctive histologic and developmental characteristics. Occurrence of duct obliteration and periductal elastosis in different cancer types was in the following order: cribriform cancer less than solid cancer less than tubular cancer less than infiltrating lobular cancer. Most obliterated milk ducts with periductal elastosis were located at the center of the tumor only (54/70), whereas a few were found both at the center and the periphery (16/70). Carcinomatous duct epithelium was found in small residual lumina of the obliterated ducts in 68 tumors. This finding suggests that duct obliteration with periductal elastosis is a process that develops before the carcinoma. Cicatrization of ducts apparently precedes invasive tumor growth; the process is morphologically identical in both age groups of women studied, and may be endocrine-influenced. (24 Refs)

3. A CONTRIBUTION TO THE NATURAL HISTORY OF BREAST CANCER. II. PRECURSORS AND LESIONS ASSOCIATED WITH SMALL CANCERS OF THE BREAST.

Egger H, Tulusan AH, Schneider ML
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany
Arch Gynecol; 231(3):199-208 1982

Sixty-five breast cancers of max diameter 10 mm or less were examined microscopically. The small cancers were located at the edge of the breast; near the nipples, in subcutaneous fat or close to the pectoral fascia. All lesions, except a colloid carcinoma 10 mm in diameter, showed lobular and/or duct carcinomas in situ when only the vicinity of invasive tumor was examined. The most frequent lesion was in situ duct carcinoma (49/65). Differentiation types were tubular (26), solid (20), tubular and solid (12), Indian file (4), medullary (2), and mucous (1). Obliterated mammary ducts were frequently found in the center of the small cancers. Twelve of 34 tumors with obliteration and elastosis in the tumor center showed a pre-existent stellate scar at the tumor center. Only 5/65 small breast cancers revealed metastases. The high incidence of duct carcinoma in situ (77%) suggests that most breast carcinomas originate in the duct epithelium. While scarring of ducts (obliteration) and periductal elastosis are not necessarily causally related to cancer, they do define a site of active transformation within the breast and have a clear relation to the location of many breast carcinomas. Invasive tubular components were found in all small breast cancers with duct obliteration and periductal elastosis; the lack of tubular differentiation in most large breast cancers seems very likely due to its loss during cancer growth. (27 Refs)

4. A CONTRIBUTION TO THE NATURAL HISTORY OF BREAST CANCER. III. CHANGES IN THE BASEMENT MEMBRANES IN BREAST CANCERS WITH STROMAL MICROINVASION.

Tulusan AH, Grunsteidel W, Ramming I, Egger H
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany
Arch Gynecol; 231(3):209-218 1982

Alterations of the basement membrane and basal lamina were observed in 28 small breast cancers and 17 other breast cancer specimens using electron microscopy and special staining techniques. Invasion occurred as bud-like protrusions of intraduct cancer with disruption of basement membranes at the point of invasion or extensive basement membrane defects with single cancer cell invasion. Invasive cancer originates from intraduct or lobular carcinoma in situ; alterations in basement membranes are more important than those in the basal lamina. (14 Refs)

5. CONTRIBUTIONS TO THE NATURAL HISTORY OF BREAST CANCER. IV. LOBULAR CARCINOMA IN SITU AND ITS RELATION TO BREAST CANCER.

Tulusan AH, Egger H, Schneider ML, Willgeroth F
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany
Arch Gynecol; 231(3):219-226 1982

Tissue samples from 52 patients with lobular carcinoma in situ (LCIS) were examined by histological methods and specimen radiography; tissue samples from both breasts were available from 46 patients. Of 18 breast cancers diagnosed in the 52 patients, nine were detected only after diagnosis of LCIS. There were 43 patients for whom a diagnosis of LCIS led to further surgical procedures. Six invasive cancers were detected during these procedures; four in the ipsilateral breast and two in the contralateral breast. Three further invasive cancers were discovered at 4, 7, and 10 yr after biopsy diagnosis of LCIS. Five of the six invasive cancers discovered with 24 mo after diagnosis of LCIS were clinically and mammographically occult. Of the three invasive cancers detected more than 24 mo after biopsy, only one was occult. None of the patients with invasive cancer detected after a diagnosis of LCIS had metastases in regional lymph nodes, and there were no recurrences during the short follow-up period of 1-5 yr. Since the number of invasive cancers found within 24 mo was almost half the number expected to develop cancer within 30 yr after LCIS, estimates of the time required for a microscopic lesion to become a clinically detectable tumor may need to be revised. (13 Refs)

6. ARGYROPHILIC BREAST CARCINOMAS. EVIDENCE OF LACTATIONAL DIFFERENTIATION.

Clayton F, Sibley RK, Ordonez NG, Hanssen G
Dept. Pathology, LDS Hospital, 325 8th Avenue, Salt Lake City, UT, 84243
Am J Surg Pathol; 6(4):323-333 1982

Twenty unselected breast carcinomas were examined for the presence of argyrophilia, dense-core secretory granules, and lactalbumin to determine whether the secretory product of argyrophilic breast carcinomas might represent milk protein rather than neuroendocrine polypeptide hormones. None of the patients developed carcinoid syndrome during a follow-up period averaging 1 yr. All four strongly argyrophilic carcinomas contained estrogen receptors, although in two, levels were borderline. The histologic pattern, the degree of silver impregnation, and the fine structural and immunoperoxidase findings are listed. The tumors were segregated into three groups: positive lactalbumin immunoperoxidase staining with either argyrophilia, ultrastructural dense-core secretory granules or both; no lactalbumin staining but weak to moderate argyrophilia or dense-core granules by electron microscopy; and negative lactalbumin, argyrophilia, and dense-core secretory granules. Ten of the cases showed varying degrees of argyrophilia but ultrastructural evidence of dense-core neurosecretory-like granules were found in only eight of the tumors. Of the 20 cases studied, 50% demonstrated varying degrees of argyrophilia and 65% contained dense-core, secretory granules. While immunoperoxidase staining for insulin, glucagon, ACTH, gastrin, calcitonin, somatostatin, prolactin, and pancreatic polypeptide were all negative in the five strongly argyrophilic cases, specific intracytoplasmic round granular staining for lactalbumin was found in all five tumors. The common occurrence of argyrophilia and dense-core secretory granules in breast carcinoma and lactating breast was demonstrated. (25 Refs)

7. NUCLEAR FEULGEN DNA CONTENT AND NUCLEAR SIZE IN HUMAN BREAST CARCINOMA.

Fossa SD, Marton PF, Knudsen OS, Kaalhus O, Bormer O, Vaage S
General Dept., Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Oslo, Norway
Hum Pathol; 13(7):626-630 1982

Biopsy specimens from 29 patients with operable breast carcinomas were examined by Feulgen-DNA microspectrophotometry. A diploid DNA stemline was found in 10 tumors, 7 of which were Stage I carcinomas. In 19 tumors, 10 of which were Stage II cancers, a non-diploid DNA stemline was observed. The diploid tumors were most often estrogen receptor-positive (9 of 9 examined carcinomas), whereas 13 of 19 non-diploid carcinomas studied did not contain estrogen receptors. The mean nuclear size of the non-diploid tumor cells was increased compared with that of the diploid malignant cells. Three Grade I carcinomas were diploid, whereas three Grade III tumors were non-diploid. Of the 23 Grade II carcinomas, 7 were diploid and 16 non-diploid. (Author abstract) (22 Refs)

8. AN IMMUNOCYTOCHEMICAL STUDY OF ALPHA-LACTALBUMIN IN HUMAN BREAST TISSUE.

Bailey AJ, Sloane JP, Trickey BS, Ormerod MG
(c/o Sloane) Dept. Histopathology, Royal Marsden Hosp., Sutton, Surrey, England
J Pathol; 137(1):13-23 1982

The distribution of alpha-lactalbumin (ALA) in human breast tissue was investigated by the indirect immunoperoxidase technique on paraffin embedded sections with reference to different stages of pregnancy and lactation and various pathological conditions. Hematoxylin and eosin sections from 188 patients were examined; sections from 115 of the patients were selected for immunoperoxidase staining for ALA. The absence of ALA from all the 44 breast carcinomas studied suggested that ALA has no role to play as a marker in the histopathological diagnosis or clinical monitoring of the disease. (18 Refs)

9. BREAST METASTASES FROM EXTRAMAMMARY MALIGNANCIES.

Bohman LG, Bassett LW, Gold RH, Voet R
(c/o Bassett) Dept. Radiological Sciences, Univ. California Los Angeles Center Health Sciences, Los Angeles, CA, 90024
Radiology; 144(2):309-312 1982

Metastatic foci to the breast from a wide variety of primary malignancies appear on mammograms as circumscribed spheroid shadows with only slightly irregular margins, and without evidence of microcalcifications, spiculations, or other signs of desmoplastic response that characterize many primary scirrhous carcinomas. In the cases studied, there was close correlation between the size of the metastatic lesion at palpation and mammography, a feature also characteristic of the well-circumscribed carcinomas. This is not the case with most scirrhous breast carcinomas, whose associated desmoplastic reaction results in an apparent larger size by palpation than observed on mammography. (Author abstract) (8 Refs)

10. DIAPHANOGRAPHY: A FOURTH DIMENSION IN THE DIAGNOSIS OF BREAST CANCER?

Girolamo RF, Leis HP
Inst. Breast Diseases, New York Medical Coll., Valhalla, NY
Breast; 8(2):16-21 1982

Diaphanography is discussed with respect to equipment and technique, interpretation, and clinical application for diagnosis of breast disease. The technique involves infrared recording of transillumination of the breast and consists of two parts: diaphanoscopy followed by diaphanography. Patients studied were examined clinically, followed by diaphanography (82.6%), thermography (65.2%), and mammography (99.4%). Twenty-four had biopsies and confirming pathologic diagnoses. Most of the 336 patients were between 30 and 50 yr old and fibrocystic disease and high-risk factors predominated. In two patients, breast cysts which were clinically palpable as small nodules were not observed with diaphanography because the cyst transilluminated the same as the surrounding parenchyma. In one case of lobular carcinoma in situ, one with marked apocrine metaplasia, and two with proven precancerous mastopathy, in whom mammography was inconclusive, diaphanography revealed the lesions. Accuracy of diaphanography in the differential diagnosis of benign vs malignant lesions was comparable to mammography. However, the advantage of diaphanography is that radiation is not involved and it can be used for young patients. Present applications include differentiation of cysts from solid masses, differentiation of benign from malignant lesions (82-85% accuracy), evaluation of high-risk patients, evaluation of severe dysplastic breasts, and evaluation of intermediate areas on mammography. Future applications may involve identifying a high-risk pattern and screening diagnostic examinations. (7 Refs)

11. LESER-TRELAT SIGN IN MOTHER AND DAUGHTER WITH BREAST CANCER.

Lynch HT, Fusaro RM, Pester JA, Lynch JF

Dept. Preventive Medicine, Creighton Univ., 2500 California St., Omaha, Nebraska, 68178

J Med Genet; 19(3):218-221 1982

The Leser-Trelat sign is the sudden appearance and rapid increase in size and number of seborrheic keratoses in association with cancer. Twenty cases of this unusual phenomenon have so far been reported in the world literature. More than half involve adenocarcinomas and none was shown to be familial. We report a unique example of a 41-year-old black female and her 74-year-old black mother, both of whom have demonstrated classical clinical-pathological evidence of the Leser-Trelat sign and adenocarcinoma of the breast. The remainder of the family history was negative for cutaneous lesions and cancer. The etiological and pathogenetic significance of the Leser-Trelat sign in association with carcinoma of the breast in this mother and daughter remains obscure. (Author abstract) (5 Refs)

12. THE SIGNIFICANCE OF MAMMOGRAPHY IN FOLLOW-UP CARE OF MAMMARY CARCINOMA PATIENTS FOR DETECTION OF BILATERAL CARCINOMA.

Schalldach U, Schumann E

Radiologische Klinik und Poliklinik, Medizinische Akademie, Nordhauser Str. 74, DDR-5060 Erfurt, E. Germany

Zentralbl Chir; 107(8):462-467 1982

The occurrence of bilateral mammary carcinoma was studied in 651 women undergoing clinical and mammographic examination. Indications of carcinoma were found in 28 women, of whom 15 had suspicious clinical and mammographic findings and 13 had only suspicious mammographic findings. Diagnosis of carcinoma was confirmed in 13 of the women (7 with suspicious clinical and mammographic findings and 6 with normal clinical findings). Three of the women had benign tumors (1 woman with suspicious clinical and mammographic findings and 2 with normal clinical findings). Twelve of the women with suspicious findings did not undergo surgery; 11/12 had generalized tumor (skin, lung, or bone metastases), and 1/12 was too old for surgery. Simultaneous bilateral carcinomas were found in four of the women; all of these tumors were occult. Metachronous bilateral carcinomas were found in 10 of the women; tumors in 8/10 were clinically evident, and those in 2/10 were occult. Metastases in the contralateral breast were found in 11 of the women; 6/11 were occult. All tumors and metastases detected in the study were detected by mammography. Mammography can detect tumors and metastases before they are clinically manifest and is, therefore, important in monitoring women for mammary carcinoma. Mammography is recommended prior to therapy, at mo 6 and 12 after therapy, and at 1-yr intervals thereafter. (11 Refs) (In GER)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

13. THE SPECIFIC BINDING OF ESTRADIOL AND ESTRONE AND THE SUBSEQUENT DISTRIBUTION OF ESTROGEN-RECEPTOR COMPLEXES WITHIN MCF-7 HUMAN BREAST CANCER CELLS.

MacIndoe JH, Woods GR, Etre LA

Dept. Internal Medicine, Veterans Admin. Medical Center, Iowa City, IA, 52240

Steroids; 39(3):245-258 1982

We have examined the specific binding of estradiol (E2) and estrone (E1) within MCF-7 cells using both cytosol and whole cell suspension binding assay techniques. The results of these studies have revealed that each of these estrogens binds with high but different affinity to the same single class of cytosol receptor (ER). The incubation of intact cells with E2 at 37 C resulted in the rapid formation, nuclear binding, and nuclear processing of E2-ER complexes. Reductions of incubation temperature to 15 C and 4 C resulted in slowed but continued E2-ER formation and nuclear binding, and in a marked inhibition of nuclear receptor processing. The incubation of intact cells with E1 at 37 C also was associated with the formation, nuclear binding, and nuclear processing of estrogen-ER complexes. Interestingly, however, E2 rather than E1 represented the major species of specifically bound estrogen under these conditions. This observation suggests that the estrogenic action of E1 in MCF-7 cells may be mediated largely by the intracellular formation of E2. This phenomenon provides a likely explanation of the unexpected potency of E1 in this system previously observed by other workers. Furthermore, our results suggest that E1 may represent a major source of estrogenic stimulation for some hormone-dependent human breast tumors. (Author abstract) (7 Refs)

14. STEROID HORMONE PROFILES IN WOMEN TREATED WITH AMINOGLUTETHIMIDE FOR METASTATIC CARCINOMA OF THE BREAST.

Samojlik E, Santen RJ, Kirschner MA, Ertel NH

Dept. Medicine, Veterans Admin. Medical Center, East Orange, NJ, 07019

Cancer Res; 42(8,Suppl):3349s-3352s 1982

Recent evidence suggests that aminoglutethimide (AG), a known inhibitor of adrenal steroidogenesis, is a potent blocker of aromatase and thus of estrogen production. These properties of AG have been exploited clinicaly to reduce the biosynthesis of adrenal estrogen precursors and extraglandular estrogen production in postmenopausal women with metastatic breast carcinoma. In this study, we have explored the effects of AG on a variety of steroids, including delta(5)-C19 and -C21 compounds and delta(4)-C19 and -C21 steroids as well as plasma and urinary estrogens in a series of postmenopausal women with breast cancer treated for 2 to 26 wk. Plasma concentrations of delta(5)-C21 and -C19 compounds were reduced three- to five-fold during AG therapy and remained suppressed over the duration of the study. By contrast, the delta(4)-steroids such as progesterone, androstenedione, and 17alpha-hydroxyprogesterone rose 2-to 10-fold during the initial 2 wk of AG treatment and then fell back to starting levels or were suppressed. Plasma levels of the potent androgens testosterone and dihydrotestosterone were relatively preserved during AG therapy. The possible contribution of the postmenopausal ovary to the above hormone levels during AG therapy was examined by comparing steroid values from surgically castrated and spontaneously menopausal women. No statistically significant differences between the two groups were observed. In response to AG therapy, plasma levels of estrone and estrone sulfate were decreased 61 to 72%, and urinary estrone similarly fell 85% over the 12-wk period. Estradiol concentrations in urine and plasma were similarly reduced 40 to 66% from basal values over this same period. (Author abstract) (21 Refs)

15. EVALUATION OF 5'-NUCLEOTIDE PHOSPHODIESTERASE ISOZYME-V AS A PREDICTOR FOR LIVER METASTASIS IN BREAST CANCER PATIENTS.

Tsou KC, Lo KW, Rosato EF, Yuk A, Enterline H, Schwegman C
1515 Ravdin Inst., Hosp. Univ. Pennsylvania, 3400 Spruce St., Phila, 19104
Cancer; 50(2):191-196 1982

The compound 5'-nucleotide phosphodiesterase isozyme-V (5'-NPD-V) was evaluated in 85 biopsy proven breast cancer patients as a potential marker for early liver metastasis. It correctly predicts liver metastasis in 85.7% patients with abnormal radiologic liver scan and 100% other patients with palpable liver. Serum glutamic-oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase (AP) and total bilirubin (B) were also determined in 79 of these patients as routing liver function tests (LFT). Forty-one out of 79 from this group had all four markers all within normal limits. Yet of the 41 patients, 12 patients were found positive for 5'-NPD-V. Of these 12, one was found to have liver metastasis at surgery and one had abnormal liver scan. Five other patients had liver dysfunction and one had been diagnosed as an alcoholic. Four others had no evidence of either liver problems or liver metastasis, but follow-up data were lacking. This retrospective study, therefore, suggests that there is a definite advantage to include the 5'-NPD-V in the liver profile studies for breast cancer patients, although a positive 5'NPD-V may only indicate liver repair or liver regeneration. Long-term prospective studies of these tests with breast cancer patients should be worthwhile. No relation was found between 5'-NPD-V and axillary lymph node involvement or the estrogen receptor status of the excised tumor. Thus there is no evidence currently that the appearance of the 5'-NPD-V in serum is related to lymph node metastases or hormonal control. (Author abstract) (43 Refs)

16. PROGNOSTIC SIGNIFICANCE OF THE STEROID RECEPTOR CONTENT IN PRIMARY BREAST CANCER.

von Maillot K, Horke W, Prestele H
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany
Arch Gynecol; 231(3):185-190 1982

Estrogen receptor (ER) and progesterone receptor (PR) contents in the primary tumor, involvement of axillary lymph nodes, and menopausal status were studied in relation to recurrence and survival rates in 222 patients with primary breast cancer. Women whose primary tumor showed no ERs or PRs developed recurrent disease earlier, and in the first 5 yr, more frequently. With a median period of observation of 46 mo, the recurrence rate for ER-positive cases (36%) was about equal to that for ER-negative cases (39%), but the free interval (time between mastectomy and appearance of recurrence) was markedly shorter for patients with receptor-negative tumors. Even after 6.5 yr, the survival rate for patients with ER-positive tumors was better than for those with ER-negative tumors; a similar trend seemed apparent in relation to PRs. Survival and recurrence rates seem to be more favorable for patients with estrogen receptor-positive breast cancer. This expectation applies only for patients who receive no further treatment or who continue on a given therapy. (14 Refs)

17. URINARY ANDROGEN METABOLITES AND RECURRENCE RATES IN EARLY BREAST CANCER.

Thomas BS, Bulbrook RD, Hayward JL, Millis RR
Imperial Cancer Res. Fund, P.O. Box 123, London WC2A 3PX, England
Eur J Cancer Clin Oncol; 18(5):447-451 1982

Androsterone and aetiocholanolone was measured in urine specimens obtained from 218 women with early breast cancer. Patients who excreted less than the median amount of these steroids had a significantly higher recurrence rate (p less than 0.005) than patients excreting more than the median value. The relationship between androgen excretion and recurrence is stronger in pre-menopausal women than in the post-menopausal group. The androgen assays are still associated with recurrence rates when patients are stratified by pathological stage, but no clear relationship was found with histological grade. (Author abstract) (23 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

18. SERA FROM BREAST CANCER PATIENTS CONTAIN AN IGA ANTIBODY TO A BREAST CYST FLUID COMPONENT.

Witkin SS, Richards JM, Bongiovanni AM, Breed CN, Day NK
Dept. Obstetrics and Gynecology, Cornell Univ. Medical Coll., New York, NY, 10021
Clin Immunol Immunopathol; 23(2):358-365 1982

We have previously demonstrated that aspirated breast cyst fluids from women with benign breast disease contained a particulate component (BCF-PC) that reacted with antiserum to the murine mammary tumor virus (MuMTV). Since women with breast cancer contain antibodies and antigens reactive with MuMTV it was of interest to measure the immune response in breast cancer patients to the BCF-PC. Sera were obtained from breast cancer patients prior to surgery and 5 days postmastectomy, from women with benign breast disease and from healthy women. Analysis for antibody to the BCF-PC was by an enzyme-linked immunosorbent assay. IgA from premastectomy breast cancer patients was significantly more reactive with the BCF-PC than was IgA from women in the other categories (p less than 0.001). In contrast, IgG binding to the BCF-PC did not differ among the various groups. It was further demonstrated that the reactivity of IgA from any particular serum for the BCF-PC remained constant for different BCF-PC isolates. Other fractions of breast cyst fluids were unreactive with IgA from breast cancer patients. Determination of serum IgA levels in these women revealed that the mean IgA level was significantly higher in healthy women than in the other categories (p less than 0.001). Individual IgA levels and levels of IgA antibody to the BCF-PC were found to be not correlated in breast cancer patients. These results indicate that the production of a specific IgA antibody to the BCF-PC increases in sera of patients with breast cancer. Lastly, it was shown that preincubation of patients' sera with disrupted MuMTV, but not intact MuMTV, severely reduced subsequent IgA binding to the BCF-PC. The analysis of sera for IgA antibody to the BCF-PC may be of value for the detection of breast cancer or its recurrence. (Author abstract) (20 Refs)

19. THE DETECTION OF ANTIBODIES IN BREAST CANCER PATIENT SERA TO TEN BREAST CANCER CELL LINES USING ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY.

Pizin MJ, Whitehead RH, Jose DG
Clinical Immunology and Immunogenetics Unit, Cancer Inst., Melbourne 3000, Australia
Clin Immunol Immunopathol; 23(2):392-399 1982

A total of 10 breast cancer and 7 control cell lines have been used as target cells in ADCC tests to detect antibodies to surface antigens of these cell lines using sera from 125 breast cancer patients and 109 controls. Five of the breast cancer cell lines elicited some breast cancer-associated activity. Significantly more breast cancer patient sera reacted with PMC9, 47% (p less than 0.001) and MDA-MB157, 48% (p less than 0.025) than other cancer patient or normal sera. Breast cancer patient reactivity to PMC42, 41% and MDA-MB231, 37%, was significantly (p less than 0.05) greater than that of normal sera, and greater, but not significantly different, than that of other cancer patients. Five other breast cancer cell lines HS578T, MDA-MB415, BT20, T47D, and MCF-7 elicited reactivity which was similar for all serum groups. Reactivity of breast cancer sera to control cell lines was significantly (p less than 0.05) lower than to PMC9. Patterns of breast cancer reactivity against a panel of breast cancer cell lines varied, suggesting incomplete cross-reactivity between surface antigens of breast cancer cell lines. Absorption studies of breast cancer sera with a breast cancer cell line indicated that there are a number of surface antigens present on these cell lines which are recognized by breast cancer sera. (Author abstract) (31 Refs)

20. THE IMMUNOHISTOCHEMICAL REACTIVITY OF A HUMAN MONOCLONAL ANTIBODY WITH TISSUE SECTIONS OF HUMAN MAMMARY TUMORS.

Teramoto YA, Mariani R, Wunderlich D, Schlom J
(c/o Schlom) Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Cancer; 50(2):241-249 1982

Human monoclonal antibodies have been generated following the fusion of human lymphocytes (obtained from axillary lymph nodes of mastectomy patients) with a murine nonimmunoglobulin secreting myeloma cell line. We report a detailed analysis of the reactivity of a human IgM monoclonal antibody secreted by one of these double cloned hybridoma cell lines. Tissue sections of both malignant and benign human mammary tumors, as well as apparently normal tissues, were tested using the immunoperoxidase technique and the human monoclonal antibody. Eighty-one per cent (54/67) of primary malignant mammary tumors, 100% (20/20) of metastatic breast lesions, and 14% (3/22) of benign breast lesions reacted positively with a moderate or strong intensity. The per cent of mammary carcinoma cells that stained and the pattern of staining varied among different tumor samples. While reactivity was observed with selected carcinomas of nonbreast origin, little or no reactivity was observed with apparently normal human tissues including normal mammary epithelium. The antibody reactivity observed was shown to be clearly distinct from those of both anti-T and anticarcinoembryonic antigen sera. (Author abstract) (19 Refs)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

21. LEUKOCYTE-DERIVED INTERFERON (ALPHA) IN HUMAN BREAST CARCINOMA. THE AMERICAN CANCER SOCIETY PHASE II TRIAL.

Borden EC, Holland JF, Dao TL, Gutterman JU, Wiener L, Chang YC, Patel J
K4/414, Wisconsin Clin. Cancer Center, 600 Highland Ave., Madison, WI, 53792
Ann Intern Med; 97(1):1-6 1982

A multi-institutional trials program was initiated to define the effects of interferons in disseminated human breast carcinoma. Interferon alpha, prepared from buffy coats, was administered intramuscularly at 3 X 10(6) U daily for an initial period of 28 days. Of 23 patients who entered the program, five had an objective partial response of 92 days mean duration at diverse sites of involvement. Patients who responded were significantly older ($p = 0.050$) than nonresponders. Dose escalation in eight patients did not result in any clear evidence of additional responses. Major toxicities were fatigue, anorexia with weight loss, and reversible leukopenia (less than 3.5 X 10(9) leukocytes/L in 16 patients). Natural killer cell and antibody-dependent cell-mediated cytotoxicity were significantly (p less than 0.05) enhanced 48 hr after interferon administration began but subsequently declined despite continued therapy. Serum beta2-microglobulin concentrations increased on Day 15 (p less than 0.05) and remained significantly elevated on Day 22 (p less than 0.005). Peak interferon titers (mean, 62 U) occurred 6 hr after interferon was started, varied widely between patients, and were higher and more persistent with dose escalation. Once an optimal dose is defined, prospectively randomized trials will define what role interferons may have in systemic therapy of breast carcinoma. (Author abstract) (29 Refs)

22. A RANDOMIZED STUDY OF COMBINATION CHEMOTHERAPY (VAC-FMC) WITH OR WITHOUT IMMUNOSTIMULATION BY CORYNEBACTERIUM PARVUM IN METASTATIC BREAST CANCER.

Fritze D, Becher R, Massner B, Kaufmann M, Bruntsch U, Gallmeier WM, Mayr AC, Drings P, Abel U, Edler L, Jungi WF, Queisser W, Senn HJ
Med. Univ.-Klinik, Bergheimer Str. 58, D-6900 Heidelberg, W. Germany
Klin Wochenschr; 60(12):593-598 1982

A total of 156 patients with metastatic breast cancer were entered into a prospective multicenter trial in September 1975. All patients were treated monthly with vincristine, adriamycin and cyclophosphamide (VAC) six times, followed by 5-fluorouracil, methotrexate and cyclophosphamide (FMC) until progression was documented. By random assignment, the patients received 5 mg/m2 Corynebacterium parvum (CP) subcutaneously on Day 1, in addition to VAC/FMC. Of the 150 evaluable patients, 33 of 76 (45%) and 36 of 74 (49%) had complete or partial response to VAC/FMC plus CP, respectively. The Kaplan-Maier curves of duration of remission and survival were almost identical (medians 14.5 vs 12.1 mo and 22.2 vs 21.1 mo, respectively). The hematologic and gastrointestinal toxicity were also similar in the two study groups. However, 19 of 74 (26%) patients developed skin ulcers after repeated injections of CP. These patients showed prolonged survival ($p = 0.002$, log rank test). These results suggest that adding nonspecific immunostimulation with CP to currently available chemotherapy on Day 1 is of no benefit to most patients with metastatic breast cancer, but may select an 'immunoreactive' subgroup with increased local toxicity and survival. (Author abstract) (12 Refs)

23. MITOXANTRONE: A PHASE II STUDY IN THE TREATMENT OF PATIENTS WITH ADVANCED BREAST CARCINOMA AND OTHER SOLID TUMORS.

Stuart-Harris RC, Smith IE
Dept. Medicine, Royal Marsden Hosp., Fulham Road, London SW3, England
Cancer Chemother Pharmacol; 8(2):179-182 1982

Initial experience with a phase II study of Mitoxantrone (MXT), 1,4-dihydroxy-5,8-bis-2-2-hydroxyethyl-amino-ethyl amino 9,10-anthracenedione dihydrochloride, in the treatment of 34 patients with advanced breast and other solid tumors, is reported. Twenty-nine patients had breast carcinoma, three had small cell lung cancer and one had squamous cell carcinoma of the bronchus and colonic carcinoma. Phase I clinical trials had shown the dose-limiting toxicity to be leukopenia, and indicated a starting dose of 12-14 mg/square meter every 3 wk. Eight of the 29 patients with advanced breast cancer achieved a partial response; none achieved a complete response. Two further patients achieved minor responses in soft tissues. Five/eight patients achieving partial response had received no prior chemotherapy. Response was achieved within 3 wk in three patients, 6 wk in two patients, 9 wk in two patients, and 12 wk in one patient. Median duration of response has not yet been determined but will be in excess of 5 mo. One of six adriamycin non-responders responded to MXT. MXT treatment was associated with a marked lack of serious side effects. MXT is clinically active against breast carcinoma, with response rate and duration of response as good as those reported for most other single agents with the possible exception of adriamycin. (9 Refs)

24. AMINOGLUTETHIMIDE IN THE TREATMENT OF ADVANCED POSTMENOPAUSAL BREAST CANCER.

Harris AL, Powles TJ, Smith IE
Royal Marsden Hosp., Fulham Road, London SW3 6JJ, England
Cancer Res; 42(8,Suppl)::3405s-3408s 1982

A group of 213 unselected postmenopausal women with advanced breast cancer were treated with aminoglutethimide, 250 mg 4x a day, and hydrocortisone, 20 mg 2x a day. Follow-up is 10 mo to 4 yr from the start of treatment. In 190 assessable patients, there were 6 complete responses (CR), 47 partial responses (PR), 25 stable disease (SD), and 3 mixed responses. Overall objective response rate was 28% and with SD was 41%. Median duration of objective response was 14 mo. Objective response by site was: soft tissue, 31%; nodes, 27%; bone 23%; liver, 22%; and lung, 16%. A further 32% of patients with bone deposits had SD, and 19 of 60 patients with progressive disease had pain relief. Years after menopause, age and tumor-free interval did not affect response rates. Thirty-eight per cent of patients responding to previous endocrine therapy responded to aminoglutethimide compared with 19% of patients who had progressed on previous endocrine therapy. A group of 213 patients were assessable for toxicity. Main side effects were drowsiness (33%), rash (23%), and nausea (15%). Eleven patients stopped treatment because of toxicity. Median survival from start of treatment was 28 mo for PR-CR and for SD and 10 mo for progressive disease (p less than 0.001). Median survival from first metastasis was 43 mo for PR-CR, 40 mo for SD (not significantly different), and 22 mo for progressive disease (p less than 0.001). Aminoglutethimide is an effective endocrine therapy in advanced postmenopausal breast cancer, particularly for bone deposits. Disease stabilization is associated with symptomatic and survival benefit similar to CR-PR. (Author abstract) (22 Refs)

25. ADEQUACY OF ESTROGEN SUPPRESSION WITH AMINOGLUTETHIMIDE AND HYDROCORTISONE AS TREATMENT OF HUMAN BREAST CANCER: CORRELATION OF HORMONAL DATA WITH CLINICAL RESPONSES.

Santen RJ, Worgul TJ, Samojlik E, Boucher AE, Lipton A, Harvey H
Dept. Medicine, Div. Endocrinology and Oncology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(8,Suppl):3397s-3401s 1982

Human breast neoplasms can be divided into hormone-dependent and hormone-independent subtypes. Estrogen is the major hormonal stimulus for growth of the dependent tumors. Failure to respond to estrogen suppression therapy could reflect either an incomplete lowering of estrogens or the hormonal independence of the tumor. We compared the levels of several estrogens and other hormones in women experiencing objective responses and disease progression during therapy with the aromatase-steroidogenesis inhibitor, aminoglutethimide, and replacement hydrocortisone. Pretreatment hormonal profiles of the estrogens, androgens, ketosteroids, thyroxine, polypeptide hormones, and carcinoembryonic antigen did not differ significantly among response groups. During treatment, the levels of all estrogens were suppressed to a similar degree in the progression group and in the responders. Data suggested that lack of estrogen suppression did not explain the response to treatment in the patients receiving aminoglutethimide-hydrocortisone. This finding differs from our results in a similarly analyzed control group of patients treated with surgical adrenalectomy. Levels of the weak androgens, dehydroepiandrosterone sulfate and androstenedione, were found to be higher in the progression group compared to the responders. This observation could not be explained by differences in duration of treatment between groups. Analysis at 1 to 12 wk, 13 to 24 wk, and 25 to 36 wk after initiating treatment indicated higher androgen levels at each time point in the progression group. While the finding of higher androgen levels in the responder group remains unexplained, this study indicates that incomplete estrogen suppression is not responsible for lack of tumor response in patients with progressive disease during aminoglutethimide-hydrocortisone therapy. (21 Refs)

26. USE OF AMINOGLUTETHIMIDE AS SECOND-LINE ENDOCRINE THERAPY IN METASTATIC BREAST CANCER.

Kaye SB, Woods RL, Fox RM, Coates AS, Tattersall MH
Dept. Oncology, Univ. Glasgow, Glasgow, Scotland
Cancer Res; 42(8,Suppl):3445s-3447s 1982

Sixty-five patients with advanced breast cancer, progressive despite prior endocrine therapy in all cases and prior chemotherapy in most cases, were treated with aminoglutethimide, 250 mg 4x a day. At present, 52 are evaluable for response assessment, and of these 10 (19%) showed an overall objective response, major sites of response being soft tissue and lung. A further 12 patients (23%) had stable disease during aminoglutethimide therapy while a total of 9 patients with bone metastases reported marked relief of pain without objective evidence of response. Forty-nine patients had received prior treatment with tamoxifen, and of the 10 tamoxifen responders 4 (40%) responded to subsequent aminoglutethimide, while of the 20 tamoxifen failures only 2 (10%) responded to subsequent aminoglutethimide. Aminoglutethimide was reasonably well tolerated, although six patients (9%) discontinued treatment because of intolerable side effects. Six of the 10 responding patients have subsequently relapsed, with a mean duration of response of 17 wk, but 4 continued to respond at 24, 32, 55, and 111 wk, respectively. The median survival from the start of aminoglutethimide therapy is in excess of 41 wk for responders and 11 wk for nonresponders, while the median survival from first relapse is 48 mo for aminoglutethimide responders and 28 mo for aminoglutethimide nonresponders. These results confirm that aminoglutethimide can offer a useful alternative form of endocrine therapy for advanced breast cancer, but the response rates obtained in heavily pretreated patients are inferior to those obtained when aminoglutethimide is used earlier in sequential treatment. For optimal results, particularly in terms of quality of life, aminoglutethimide should generally be used prior to chemotherapy. (Author abstract) (12 Refs)

27. CROSS-OVER COMPARISON OF TAMOXIFEN AND AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER.

Harvey HA, Lipton A, White DS, Santen RJ, Boucher AE, Shafik AS, Dixon RJ, Members of the Central Pennsylvania Oncology Group
Central Pennsylvania Oncology Group, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(8,Suppl):3451s-3453s 1982

Thirty-four postmenopausal patients with advanced breast cancer had an overall objective response rate of 47% when treated with aminoglutethimide and hydrocortisone initially and a response rate of 24% when crossed over to therapy with tamoxifen after progression on aminoglutethimide. A similar group of 32 patiens experienced a response rate of 28% when treated with tamoxifen first and a 19% objective response rate on subsequent therapy with aminoglutethimide. Patients who failed to respond to the first therapy seldom responded on cross-over to the alternate therapy. Toxicities were acceptable with both forms of therapy. Tamoxifen and aminoglutethimide used sequentially are effective forms of palliative hormonal therapy in metastatic breast cancer. (Author abstract) (8 Refs)

28. TAMOXIFEN VERSUS AMINOGLUTETHIMIDE VERSUS COMBINED TAMOXIFEN AND AMINOGLUTETHIMIDE IN THE TREATMENT OF ADVANCED BREAST CARCINOMA.

Smith IE, Harris AL, Morgan M, Gazet JC, McKinna JA
Breast Unit, Royal Marsden Hosp., Fulham Road, London SW3 6JJ, England
Cancer Res; 42(8,Suppl):3430s-3433s 1982

In a control randomized cross-over trial, 117 patients with advanced breast cancer were treated initially either with tamoxifen (10 mg po twice daily) or aminoglutethimide (250 mg po 4x daily) with hydrocortisone (20 mg twice daily). Patients failing to respond or relapsing were switched to the alternative treatment. Eighteen (30%) of the 60 patients initially treated with tamoxifen achieved an objective response, and 11 (18%) achieved stable disease. Seventeen (30%) of the 57 patients treated initially with aminoglutethimide achieved an objective response, and 13 (23%) achieved stable disease. Aminoglutethimide achieved a 35% objective response and a further 26% subjective bone pain relief in patients with bone metastases (overall, 61%) compared with a 17% objective response and a further 17% objective bone pain relief with tamoxifen (total, 34%). None of six premenopausal patients responded to aminoglutethimide compared with two of four responding to tamoxifen. The median response duration to aminoglutethimide was 16 mo compared with 20 mo for tamoxifen. Side effects for aminoglutethimide (including lethargy, rash, and depression) were more common than for tamoxifen, and 7% of aminoglutethimide-treated patients had to discontinue treatment because of these compared with 0% on tamoxifen. In cross-over studies, 6 of 12 tamoxifen responders who relapsed achieved a second response to aminoglutethimide (50%), as did 6 of 29 patients who initially failed to respond to tamoxifen (21%). In contrast, none of 11 patients relapsing after response to aminoglutethimide achieved a second response to tamoxifen; only 1 of 18 nonresponders to aminoglutethimide subsequently responded to tamoxifen (6%). In a subsequent study in which 62 patients were treated with combined tamoxifen and aminoglutethimide, the overall response rate of 37% was not significantly better than that for either agent used alone. (Author abstract) (12 Refs)

29. AMINOGLUTETHIMIDE IN TAMOXIFEN-RESISTANT PATIENTS: THE MELBOURNE EXPERIENCE.

Murray RM, Pitt P
Endocrine Unit, Cancer Inst., Melbourne, Victoria, Australia
Cancer Res; 42(8,Suppl):3437s-3441s 1982

A group of 160 women with actively progressing metastatic breast cancer were treated with aminoglutethimide to induce medical adrenalectomy. The degree of adrenal suppression was monitored by measurement of dehydroepiandrosterone sulfate levels, and classification of response was carried out according to UICC criteria by two observers. Assessment of response is available for 136 patients, and of these 50 (36.7%) had an objective remission. In an additional 10 patients, the disease became static. Mean remission duration is 12.5 mo (range, 4 to 30). Forty-one patients had previously remitted to tamoxifen and then relapsed, and of these 22 (53.6%) experienced another remission with aminoglutethimide. Fifty patients had failed to respond to tamoxifen, and of these 16 (32%) had a remission with aminoglutethimide. In the 20 patients who did not receive tamoxifen and in the 25 whose response to it could not be classified, the remission rates to aminoglutethimide were 25 and 28%, respectively. The high remission rate to medical adrenalectomy in patients who have previously responded to tamoxifen makes it the treatment of choice in tamoxifen-responsive patients. (Author abstract) (6 Refs)

30. RANDOMIZED TRIAL OF AMINOGLUTETHIMIDE VERSUS TAMOXIFEN IN METASTATIC BREAST CANCER.

Lipton A, Harvey HA, Santen RJ, Boucher A, White D, Bernath A, Dixon R, Richards G, Shafik A
Central Pennsylvania Oncology Group, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(8,Suppl):3434s-3436s 1982

We compared antiestrogen therapy (tamoxifen) with an estrogen suppression regimen (aminoglutethimide-hydrocortisone) in postmenopausal women with metastatic breast carcinoma. Fifteen of 39 patients (38%) who received tamoxifen experienced an objective tumor regression (3 complete, 12 partial remissions), whereas 13 of 36 women (36%) receiving aminoglutethimide responded (1 complete remission, 12 partial remissions). The median duration of response was similar. The site of tumor involvement appears to be important in choosing between these hormonal treatments. Aminoglutethimide appears to offer a greater chance of response in patients with bone involvement. (Author abstract) (18 Refs)

31. SEQUENTIAL VERSUS CONCOMITANT CHEMO-HORMONAL THERAPY IN BREAST CANCER.

Kumar KS, Vogel CL, Moore MR, Bartolucci AA
(c/o Vogel) Dept. Oncology, Univ. Miami Sch. Medicine, Miami, FL
Breast; 8(2):2-7 1982

Treatment with sequential or concomitant chemo-hormonal therapy was investigated in 44 patients (46-79 yr old) with metastatic breast cancer. None of the patients had been treated previously with hormonal therapy or chemotherapy. Twenty-one patients received sequential therapy consisting of diethylstilbestrol (DES: 5 mg po 3x/day for at least 2 mo or until disease progression occurred), withdrawal of DES, and chemotherapy followed when progression occurred [cyclophosphamide, 500 mg/square meter (m2); adriamycin, 50 mg/m2; and 5-fluorouracil, 500 mg/m2; iv every 3 wk for 9 courses (CAF)]. Concomitant therapy involved CAF on day 1, DES beginning on day 3, repeated every 3 wk for nine courses or until disease progression. Stable or responding patients were maintained on DES alone. If disease progression occurred, both DES and CAF were discontinued. The objective response rates were 56.5% for concomitant therapy and 42.8% for sequential therapy. Median duration of response was 9.8 mo for concomitant therapy and 7.7 for sequential therapy. Median survival was 20.4 mo for the concomitant group and 15.2 mo for the sequential group. No statistically significant differences were noted in overall response rate, remission duration, or survival between the two groups of patients. Six additional studies in which estrogens were combined with cytotoxic chemotherapy are reviewed. Little evidence was found that concomitant chemo-hormonal therapy for metastatic breast cancer provides an advantage over sequential therapy in patients chosen for initial hormonal therapy on the basis of receptor status, or on the basis of analysis of other prognostic variables. (73 Refs)

32. MASTECTOMY AS AN ADJUVANT TO CHEMOTHERAPY FOR LOCALLY ADVANCED OR METASTATIC BREAST CANCER.

Aisner J, Morris D, Elias G, Wiernik PH
Baltimore Cancer Res. Center, 22 S Greene St., Baltimore, MD, 21201
Arch Surg; 117(7):882-887 1982

Patients with unresectable tumors require local treatment of ulcerating or fungating masses. Chemotherapy can shrink the tumor, permitting mastectomy. Continued chemotherapy treats the overt or micrometastases. Of 27 patients with bulky primary tumors, 15 had overt metastases and 12 did not. Thirteen of the 27 had inflammatory carcinoma. After three to four chemotherapy courses, 24 patients were operable, and 22 underwent mastectomy. Eighteen of the 22 had closure without skin grafts. In three, disease recurred at the primary site, and in five at both primary and distal sites. Preoperatively, one patient (4%) achieved complete response and 19 (70%) achieved partial response. After mastectomy, five patients with metastases in stable partial response further responded to chemotherapy and achieved complete response. Chemotherapy with adjuvant mastectomy is technically feasible and offers the possibility of improved duration of survival in some patients. (Author abstract) (20 Refs)

33. CHEMOTHERAPY BEFORE AND AFTER MASTECTOMY IN STAGE III BREAST CANCER.

Perloff M, Lesnick GJ
Columbia Univ. Coll. Physicians and Surgeons, 630 W 168th St., New York, NY, 10032
Arch Surg; 117(7):879-881 1982

Seventeen patients with Stage III breast cancer were treated by modified radical mastectomy preceded and followed by multiagent cytotoxic chemotherapy. The preoperative treatment resulted in a decrease in size of the primary tumor, facilitating the subsequent surgical procedures. There were no serious surgical complications. Wound healing was uneventful. Median disease-free survival time was 29 mo and median survival time was 40+ mo. Six of the 17 patients are living free of recurrence from more than 33 to more than 79 mo after initial therapy. (Author abstract) (11 Refs)

34. BREAST CANCER: A 21 YEAR EXPERIENCE WITH CONSERVATIVE SURGERY AND RADIATION.

Clark RM, Wilkinson RH, Mahoney LJ, Reid JG, MacDonald WD
Princess Margaret Hosp., 500 Sherburne St., Toronto, Ontario M4X 1K9, Canada
Int J Radiat Oncol Biol Phys; 8(6):967-975 1982

Six hundred and eighty patients with breast cancer (pathological Stage I and II) were treated by partial mastectomy and, in some, breast irradiation, and followed for 21 yr. None of the patients had clinical evidence of nodal involvement in the axilla or supraclavicular lesions. The age distribution was typical with 23% patients 65-75 yr old at diagnosis and 24% less than 45 yr old. The overall actuarial survival at 5 yr was 78% and at 10 yr 62%. Relative survivals were 83% and 71%, respectively. In the series, 55/177 deaths (31%) were a result of causes other than breast carcinoma. The commonest cause of death was cardiac disease (30 patients). Patients 35-65 and greater than 70 yr old had the best survival. Among the 154 patients who had no radiation, 57% were pathologically T1 and 14% were T2; corresponding percentages among the 526 patients who had radiation were 43% and 23% respectively. When comparing survival with tumor size, no significant difference in survival by T stage was observed. Patients with pathological T1 tumors, however, had an actuarial survival rate of 83% at 5 yr and 63% at 10 yr. In those patients where only the breast was irradiated the relapse rate was 7.6% at 5 yr. The relapse rate was 12.3% if the breast and any nodal group was irradiated. With no radiation to the breast the relapse rate was 24.4% despite a larger proportion of patients with more favorable disease. By 10 yr the relapse rates rose to 16.3%, 21.5%, and 26.5%, in patients with irradiation to the breast only, the breast plus nodes, and in patients not irradiated, respectively. Relapse in the breast alone was not detrimental to survival if treated appropriately. These findings support conservative management of patients with operable breast cancer. (30 Refs)

35. FAVORABLE FACTORS IN THE ADJUVANT THERAPY OF BREAST CANCER.

Carpenter JT, Maddox WA, Laws HL, Wirtschafter DD, Soong SJ
Div. Hematology/Oncology, Univ. Alabama Birmingham, Birmingham, AL, 35294
Cancer; 50(1):18-23 1982

One hundred seventy-one patients received 1 yr of melphalan or intermittent cyclophosphamide, methotrexate, and fluorouracil after mastectomy for breast cancer with involved axillary nodes. Analysis with a median follow-up of 3 yr indicates a favorable outcome only for patients with one to three positive nodes who were treated with melphalan and who experienced a leukocyte count less than 3,000/mm3 (3.0 x 10(9)/1). Tumor size, av percentage of dose received, menopausal status, and type of chemotherapy were not significant factors in recurrence of disease, after adjustment of the number of positive nodes and leukocyte count nadir during treatment based on a multifactorial analysis. These data suggest that administration of a dose of melphalan which does not produce a leukocyte count of less than 3,000/mm3 is ineffective in preventing early recurrence of disease. Since oral melphalan is known to be erratically absorbed, lack of hematologic toxicity may well be due to variable absorption of the drug on a fixed-dose regimen. Failure to prevent recurrence of disease in this and other trials using oral melphalan may be due to chemotherapy-related as well as disease-related factors. (Author abstract) (21 Refs)

36. COMPARISON OF SURGICAL ADRENALECTOMY TO MEDICAL ADRENALECTOMY IN PATIENTS WITH METASTATIC CARCINOMA OF THE BREAST.

Wells SA, Worgul TJ, Samojlik E, Boucher AE, Lipton A, Harvey H, White D, Smart E, Cox C, Santen RJ
Dept. Surgery, Washington Univ. Sch. Medicine, 4960 Audubon Ave., St. Louis, MO, 63110
Cancer Res; 42(8,Suppl):3454s-3457s 1982

This study compared a form of 'medical adrenalectomy' with surgical adrenalectomy in a randomized, controlled trial. Ninety-six postmenopausal women with metastatic carcinoma of the breast were randomized to receive either surgical adrenalectomy or medical therapy po with an adrenal inhibitor, aminoglutethimide (AG) plus replacement hydrocortisone (HC). Forty medical patients and 29 surgical patients remained evaluable after inclusion into the study. None of the pretreatment variables differeed significantly between the groups of evaluable patients. Fifty-three percent of patients treated with AG plus HC had objective responses compared to 45% of patients treated by surgical adrenalectomy. An additional 5% in the surgical adrenalectomy category experienced disease stabilization. Regressions lasted 17.2 +-1.7 (S.E.) mo in the medical group and 17.1 +-2.2 in the surgical group. Median survival after objective response to AG plus HC did not differ significantly from that following surgery. Is surgical adrenalectomy superior to medical adrenalectomy? It was reasoned that AG plus HC would be preferred to surgical adrenalectomy on practical grounds if the operative method was not proved superior. The null hypothesis designed to answer this question was rejected. Therefore, the chance that surgical adrenalectomy is less than 1%. These data provide strong evidence that AG plus HC produces clinical remissions of breast carcinoma as frequently and for the same duration as does surgical adrenalectomy. (18 Refs)

37. TREATMENT FOR MENINGEAL CARCINOMATOSIS IN BREAST CANCER.

Yap HY, Yap BS, Rasmussen S, Levens ME, Hortobagyi GN, Blumenschein GR
MRCP Dept. Medicine, Medical Breast Service, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 50(2):219-222 1982

Forty breast cancer patients with meningeal carcinomatosis were treated with a combined program of whole brain irradiation therapy with intrathecal and intraventricular methotrexate and citrovorum factor rescue. Responses were seen in 26 patients (65%); 13 patients (35%) failed to respond. The median survival time for the responding patients was 6 mo, and for the nonresponders, 1 mo. Factors affecting response and survival included pretreatment spinal fluid glucose, protein, and duration of CNS-related symptomatology prior to onset of therapy. In contrast, pretreatment CSF tumor cell count, CEA and initial CNS functional status did not appear to have prognostic significance. The authors conclude that following intensive therapy there can be much improvement in the quality of life and disease-free survival in breast cancer patients with meningeal carcinomatosis. (Author abstract) (12 Refs)

SELECTED ASPECTS OF BREAST CANCER ETIOLOGY AND EPIDEMIOLOGY

38. EPIDEMIOLOGY OF BREAST CARCINOMA III: RELATIONSHIP OF FAMILY HISTORY TO TUMOR TYPE.

Rosen PP, Lesser ML, Siene RT, Kinne DW
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 50(1):171-179 1982

Previous breast carcinoma in at least one female relative was reported by 31% of 1,024 women treated consecutively for breast carcinoma at Memorial Hospital. Eighty (7.9%) of their mothers had had breast cancer. Maternal breast cancer was significantly (p less than 0.006) more frequent among women with medullary carcinoma than those with other tumor types and among those who were pre- or perimenopausal at diagnosis (p less than 0.001). Among the 727 patients who had one or more sisters, 12% had a sister who had been treated for breast cancer. The highest frequency of carcinoma in at least one sister occurred in patients with lobular carcinoma while the medullary carcinoma group had the least number of patients with an affected sister (p less than 0.03). Occurrence of breast cancer in a sister was almost twice as common in patients who were postmenopausal at diagnosis (p less than 0.005) than in premenopausal patients. When stratified by histologic type, the mean age at diagnosis of the patients did not differ appreciably from the age at diagnosis of their sisters. Detailed analyses of histologic type and other more distant familial relationships were also obtained but were considered to be less reliable because of problems in ascertainment and there were fewer affected relatives. No single histologic type of carcinoma was consistently linked to a disproportionately high or low frequency of carcinoma in all classes of relatives. It is possible that studies of family history limited to information available when the patient is first treated present an incomplete picture of familial aggregation. Further follow-up after diagnosis is needed to obtain a more reliable measure of the extent to which relatives are affected by breast cancer and patterns of family distribution associated with specific tumor types. (Author abstract) (16 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

39. AROMATASE IN HUMAN BREAST CARCINOMA.

Perel E, Blackstein ME, Killinger DW
(c/o Killinger), Univ. Toronto, Medical Sciences Building, Room 7366, Toronto, Ontario, M5S 1A8, Canada
Cancer Res; 42(8,Suppl):3369s-3372s 1982

Breast carcinoma tissue is capable of forming estrogens from circulating androgen precursors. In this study, aromatase was examined in homogenates of breast adipose and breast carcinoma tissue, in normal and abnormal parenchymal breast tissue, and in breast carcinoma cells in culture. Homogenates of carcinoma tissue showed a wide range of activity in the conversion of androstenedione to estrone. The mean conversion in carcinoma tissue was greater than that seen in parenchymal tissue from patients with gynecomastia and mammary dysplasia. Homogenates of breast adipose tissue from patients with benign and malignant disorders showed comparable aromatase activity. Three cell lines isolated from a primary breast carcinoma differed in their aromatase activity demonstrating a heterogeneity of aromatase activity in cells from a single tumor. Studies of aromatase activity in breast carcinoma cells in culture over a period of 8 hr demonstrated progressive estrone formation. Testosterone formation from adrostenedione was noted in all studies using both homogenates and cell cultures. Testosterone formation from androstenedione was approximately 10-fold greater than was the formation of estrone from androstenedione in all studies. The metabolism of androstenedione to other androgens examined in homogenates of normal and carcinomatous breast tissue revealed that the major products were androsterone, 5beta-androsterone, dihydrotestosterone, and epiandrosterone. Both estrogen and androgen formation within the cell may be important in determining the cellular response. (Author abstract) (11 Refs)

40. SIGNIFICANCE OF AROMATASE ACTIVITY IN HUMAN BREAST CANCER.

Miller WR, Hawkins RA, Forrest AP
Univ. Dept. Clinical Surgery, Medical Sch., Teviot Place, Edinburgh EH8 9AG, Scotland
Cancer Res; 42(8,Suppl):3365s-3368s 1982

The significance of in vitro aromatization of [7alpha-3H]testosterone to estradiol by human breast cancer has been investigated by correlation with (a) estrogen receptor activity and (b) clinical response to endocrine therapy. Evidence for estradiol synthesis was obtained in 66 and estrogen receptor activity in 81 of 110 tumors. Whereas most estrogen receptor-positive tumors synthesized estradiol, the majority of receptor-negative tumors did not. This tendency for aromatization to be associated with estrogen receptor-positive tumors was statistically significant (p less than 0.005). Mean level of receptor was also significantly higher in tumors with aromatization than in tumors without estradiol synthesis (p less than 0.001). Forty patients with advanced breast cancer have been treated by endocrine therapy. There was a significant trend for tumors with aromatization to be associated with response to treatment (p less than 0.05), but the correlation was not absolute and may simply reflect the association between aromatase activity and estrogen receptors. Within the small subgroup of patients treated with aminoglutethimide or adrenalectomy, tumors with high aromatase activity responded whereas those without aromatization did not. Tumor estrogen biosynthesis may therefore be of clinical significance in selecting patients for treatments which remove sources of precursor for aromatization or inhibit aromatase activity itself. (Author abstract) (24 Refs)

41. EFFECTS OF AROMATASE INHIBITOR 4-HYDROXYANDROSTENEDIONE AND OTHER COMPOUNDS IN THE 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED BREAST CARCINOMA MODEL.

Brodie AM, Garrett WM, Hendrickson JR, Tsai-Morris CH
Dept. Pharmacology and Experimental Therapeutics, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201
Cancer Res; 42(8,Suppl):3360s-3364s 1982

Aromatase inhibitor, 4-hydroxyandrostene-3,17-dione (4-OHA), is a highly effective treatment in rats with 7,12-dimethylbenz(a)anthracene-induced hormone-dependent mammary tumors. Over 90% of tumors regress to less than one-half of their original size, and a high proportion regress completely. Treatment of rats with other inhibitors, 4-acetoxyandrostene-3,17-dione and 1,4,6-androstatriene-3,17-dione produce similar results. In comparison with other aromatase inhibitors, the compounds reduced ovarian estrogen secretion in the rat to the same extent as aminoglutethimide, whereas Teslac was without effect. The latter two compounds caused little and no regression of DMBA-induced mammary tumors, respectively. Our recent studies with 4-OHA, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatriene-3,17-dione indicate that they interact with aromatase by a two-component mechanism, a rapid competitive inhibition, and a slower enzyme inactivation. Treatment of rats with 4-OHA also caused greater than 80% loss of ovarian aromatase activity in vivo and a reduction in ovarian estrogen secretion, which are maintained for at least 48 hr after injection. Although 4-OHA is cleared rapidly in vivo, the above results suggest that the compound has a sustained effect. Thus, when 7,12-dimethylbenz(a)anthracene-induced tumor-bearing rats were treated with 4-OHA injections on alternate wk, tumor regression continued to occur during wk without treatment. The overall regression was similar to that with continuous treatment. 4-OHA is also effective and similar to ovariectomy in rats with hormone-dependent metastatic mammary tumors produced by nitrosomethylurea. Our results indicate that mammary tumor regression induced by 4-OHA is mainly the result of the inhibition of aromatization, although other activities of the compound may also contribute. (Author abstract) (23 Refs)

42. A REASSESSMENT OF THE ROLE OF BREAST TUMOR AROMATIZATION.

Bradlow HL
Rockefeller Univ., New York, NY, 10021
Cancer Res; 42(8,Suppl):3382s-3386s 1982

While the role of estrogens in the maintenance of human breast carcinoma has been firmly established for many yr, the sources of this estrogen remain unresolved. Input-output analysis of steroid uptake by breast carcinomas showed no specific uptake of estrogens from blood. Based on the detection of the necessary enzyme systems, Adams and Wong proposed that breast tumors could function as 'paraendocrine organs' capable of producing sufficient estradiol (E2) to stimulate their own growth. Using the reported values for the concentration of C19 steroid precursors and the rhoTTC19-E2 values one can estimate that the contribution of in situ aromatization to the tumor estrogen pool is quite small. (Author abstract) (44 Refs)

43. CYCLIC OVARIAN FUNCTION AND BREAST CANCER.

Sherman BM, Wallace RB, Bean JA
Dept. Internal Medicine, Univ. Iowa, Iowa City, IA, 52242
Cancer Res; 42(8,Suppl):3286s-3288s 1982

We postulated previously that systematic differences in menstrual cycle length and/or variability might be used as indicators of underlying hormonal abnormalities that could help explain the endocrine biology of some breast cancer risk factors. In the present study, we prospectively and retrospectively analyzed menstrual cycle patterns in breast cancer cases and controls in two populations. No significant differences were found. This and previous studies emphasize that contemporary women have a long reproductive experience characterized by uninterrupted, regular menses, which is a condition of maximum ovulation potential and which contributes to estrogen stimulation over time. (Author abstract) (25 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abel U 22
Aisner J 32
Bailey AJ 8
Bartolucci AA 31
Bassett LW 9
Bean JA 43
Becher R 22
Bernath A 30
Blackstein ME 39
Blumenschein GR 37
Bohman LG 9
Bongiovanni AM 18
Borden EC 21
Bormer O 7
Boucher A 30
Boucher AE 25
Boucher AE 27
Boucher AE 36
Bradlow HL 42
Breed CN 18
Brodie AM 41
Bruntsch U 22
Bulbrook RD 17
Carpenter JT 35
Chang YC 21
Clark RM 34
Clayton F 6
Coates AS 26
Cox C 36
Dao TL 21
Day NK 18
Dixon R 30
Dixon RJ 27
Dressler W 2
Drings P 22
Edler L 22
Egger H 2
Egger H 3
Egger H 4
Egger H 5
Elias G 32
Enterline H 15
Ertel NH 14
Etre LA 13
Forrest AP 40
Fossa SD 7
Fox RM 26
Fritze D 22
Fusaro RM 11
Gallmeier WM 22
Garrett WM 41
Gazet JC 28
Girolamo RF 10
Gold RH 9
Grunsteidel W 4
Gutterman JU 21
Hanssen G 6
Harris AL 24
Harris AL 28
Harvey H 25
Harvey H 36
Harvey HA 27
Harvey HA 30
Hawkins RA 40
Hayward JL 17
Hendrickson JR 41
Holland JF 21
Horke W 16
Hortobagyi GN 37
Jose DG 19
Jungi WF 22
Kaalhus O 7
Kaufmann M 22
Kaye SB 26
Killinger DW 39
Kinne DW 38
Kirschner MA 14
Knudsen OS 7
Kumar KS 31
Laws HL 35
Leis HP 10
Lesnick GJ 33
Lesser ML 38
Levens ME 37
Lipton A 25
Lipton A 27
Lipton A 30
Lipton A 36
Lo KW 15
Lynch HT 11
Lynch JF 11
MacDonald WD 34
MacIndoe JH 13
Maddox WA 35
Mahoney LJ 34
Mariani R 20
Marton PF 7
Massner B 22
Mayr AC 22
McKinna JA 28
Members of the 27
Miller WR 40
Millis RR 17
Moore MR 31
Morgan M 28
Morris D 32
Murray RM 29
Ordonez NG 6
Ormerod MG 8
Patel J 21
Perel E 39
Perloff M 33
Pester JA 11
Pitt P 29
Plain MJ 19
Powles TJ 24
Prestele H 16
Queisser W 22
Ramming I 4
Rasmussen S 37
Reid JG 34
Richards G 30
Richards JM 18
Rosato EF 15
Rosen PP 38
Sacharias N 1
Samojlik E 14
Samojlik E 25
Samojlik E 36
Santen RJ 14
Santen RJ 25
Santen RJ 27
Santen RJ 30
Santen RJ 36
Schalldach U 12
Schlom J 20
Schneider ML 3
Schneider ML 5
Schumann E 12
Schwegman C 15
Senn HJ 22
Shafik A 30
Shafik AS 27
Sherman BM 43
Sibley RK 6
Siene RT 38
Sloane JP 8
Smart E 36
Smith IE 23
Smith IE 24
Smith IE 28
Soong SJ 35
Stuart-Harris R 23
Tattersall MH 26
Teramoto YA 20
Thomas BS 17
Trickey BS 8
Tsai-Morris CH 41
Tsou KC 15
Tulusan AH 3
Tulusan AH 4
Tulusan AH 5
Vaage S 7
Voet R 9
Vogel CL 31
Von Maillot K 16
Wallace RB 43
Wells SA 36
White D 30
White D 36
White DS 27
Whitehead RH 19
Wiener L 21
Wiernik PH 32
Wilkinson RH 34
Willgeroth F 5
Wirtschafter DD 35
Witkin SS 18
Woods GR 13
Woods RL 26
Worgul TJ 25
Worgul TJ 36
Wunderlich D 20
Yap BS 37
Yap HY 37
Yuk A 15

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In this issue:

- BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS) 1
- DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS 2-10
- BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS 11-17
- CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS 18
- BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY) 19-24
- REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT 25-27
- SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY) 28-31

BREAST CANCER SCREENING AND EARLY DETECTION (TECHNIQUES AND RESULTS)

1. ULTRASONIC DETECTION OF BREAST CANCER.

Kobayashi T

Sch. Medicine, Univ. Occupational and Environmental Health, Kitakyushu City, Japan

Clin Obstet Gynecol; 25(2):409-423 1982

After review of the history of breast echography, a detailed examination is presented of its use in the diagnosis of lesions of the breast. The technique of the water-bag examination of the breast is presented and the diagnostic criteria for the differentiation of benign from malignant lesions are outlined. Typical echograms are illustrated for benign cyst, fibrocystic disease, fibroadenoma and cystosarcoma phyllodes. Also illustrated are typical echograms in malignant disease, such as scirrhous and medullary carcinomas. Expanded echography improves diagnostic accuracy in early breast cancer, especially in tumors less than 2 cm. The technique for manual-scan echography is outlined. Breast echography by these methods is a noninvasive, quickly performed procedure that presents no radiation hazard

HE 20. 3173/2:

like mammography and has appreciably high diagnostic accuracy of about 85-90%. (20 Refs)

DIAGNOSIS AND PATHOLOGY OF BREAST CANCERS

2. THERMOGRAPHY IN THE DIAGNOSIS OF BREAST CANCER.

Sterns EE, Curtis AC, Miller S, Hancock JR
102 Stuart St., Kingston, Ontario K7L 2V6, Canada
Can J Surg; 25(4):412-413 1982

The value of thermography was examined in women with specific breast abnormalities as well as in those being screened. After a study of 500 patients (greater than 700 thermograms), infrared thermography was abandoned; plate thermography was continued because it demanded less technical expertise, was less expensive, and could if, reliable be applied in an office setting. In 939 patients, greater than 2,000 plate thermograms were made. Of the 939 patients, 179 had at least one abnormal thermogram but only 11/179 proved to have cancer. In follow-up studies, 74/317 patients had consistently equivocal or abnormal thermograms and 2/74 were found to have cancer during the follow-up period. When thermography was performed in 68 patients with invasive carcinoma of the breast, only 26 thermograms were abnormal. In cancers of less than 5 cm in diameter, the rate of abnormal thermograms was only 30%. In those greater than 5 cm, the rate was 66%. Abnormal thermograms were produced in 19% of 162 patients with benign lesions. The results indicated that thermography is not sufficiently refined to assist in the diagnosis or screening of breast cancer. (2 Refs)

3. BONE SCANNING AS A ROUTINE EXAMINATION OF PATIENTS WITH MAMMARY CARCINOMA; CRITICAL CONSIDERATIONS.

Heslinga JM, Pauwels EKJ, Zwaveling A
Heelkundige Kliniek, Academisch Ziekenhuis, Leiden, The Netherlands
Ned Tijdschr Geneeskd; 126(23):1036-1039 1982

One hundred and thirty-six women with breast cancer were subjected to preoperative routine bone scanning to detect skeletal metastases. Eighty-one of the 136 patients were in Columbia Stage A (median age 62 yr), 55 in Stage B/C (median age 67 yr). The scintigraphic findings were correct positive in 4/136 patients, all in Stage B/C, and false positive in eight (5/8 in Stage A and 3/8 in B/C). Fifteen of the 132 patients with negative preoperative scintigraphic findings developed skeletal metastases during the first 2 yr after surgery: 8/15 were in Stage A and 7/15 in B/C. Six of the 132 patients developed skeletal metastases 2-4 yr after surgery: 2/6 were in Stage A and 4/6 in B/C. Most of the patients with correct positive bone scans also displayed other signs of skeletal metastasis at the same time (ostealgia and increased serum alkaline phosphatase level). In view of the low incidence of skeletal metastases preoperatively and the presence of other signs of metastases routine bone scanning of breast cancer patients was abandoned both preoperatively and during the follow-up period. Bone scanning should be performed only on the basis of anamnestic date, and physical and laboratory findings. (23 Refs) (In DUT)

4. WELL-DIFFERENTIATED (TUBULAR) CARCINOMA OF THE BREAST: A CLINICOPATHOLOGIC STUDY OF 145 PURE AND MIXED CASES.

Deos PH, Norris HJ
(c/o Norris) Armed Forces Inst. Pathology, Washington, DC, 20306
Am J Clin Pathol; 78(1):1-7 1982

In this study, 145 well-differentiated (tubular) carcinomas were divided into two groups: 90 pure tubular carcinomas and 55 which were mixtures in that they contained a component of infiltrating duct carcinoma occupying less than half the tumor. Axillary lymph node metastases developed in 29% of women in the mixed group, but occurred in only 6% of the pure group. The prognosis was good in both groups, with 5-year actuarial survival rates in the pure and mixed groups of 100% and 93%, respectively. Residual carcinoma was present in the mastectomy specimen in 28% of the pure group, and in 40% of the mixed carcinomas. In addition, there was a recurrence rate of 50% in patients with pure tubular carcinoma treated by excisional biopsy. These features indicate simple excision of tubular carcinoma is likely to be inadequate therapy and that a mastectomy is warranted. Axillary node dissections should be done when there is a component of infiltrating duct carcinoma because of the increased risk of axillary lymph node metastasis. (Author abstract) (22 Refs)

5. COOPERATIVE FOLLOW-UP IN BREAST CARCINOMA.

Queisser W, Lochbuhler H, Filzmayer P, Trede M, Braun-Munzinger U, Harter G
Onkologisches Zentrum, Klinikum der Stadt Mannheim, Universitat Heidelberg, Theodor-Kutzer-Ufer, 6800 Mannheim 1, W. Germany
Dtsch Med Wochenschr; 107(23):890-895 1982

In 2 yr 359 patients with breast cancer were evaluated in a cooperative follow-up program in which the organization and documentation were done in hospital, the medial care and investigations by the family doctor. Seventy-two percent of 316 evaluable patients remained in regular control. Sixty-three percent chose the family doctor for follow-up while the others prefered hospital. In the 1st yr 71-80% attended their appointments, in the 2nd yr 60-74%. Statistically significant parameters for detection of metastases were the following: general condition, local signs, palpable lymph nodes, markedly increased ESR, alkaline phosphatase, chest radiograph, and bone scan. Cumulative freedom from recurrence in the whole group diminished from 1.0 to 0.631 in 25 mo, cumulative survival from 1.0 to 0.876 in 20 mo. In both groups there were significant differences between Stages I, II and III. Forty patients (16%) out of 250 developed a recurrence within 2.25 yr, in 4 (2%) a second carcinoma developed. There was a high proportion of local recurrences (20 out of 40) and these often led to generalized disease (11 out of 20). (Author abstract) (53 Refs) (In GER)

6. THE SIGNIFICANCE OF QUANTITATIVE BIOLOGICAL CELL PARAMETERS IN THE HANDLING OF MAMMARY CARCINOMA.

Theve NO, Azavedo E, Blomstedt B, Wilking N, Auer GU
Dept. Surgery, Sabbatsberg Hosp., Stockholm, Sweden
Acta Chir Scand; 148(3):239-241 1982

Recent work has shown that in breast cancer patients DNA measurements and estrogen receptor (ER)-analysis can contribute valuable information in the judgement of prognosis and choice of therapy. We report a case of advanced breast carcinoma with extensive liver metastases which clinically was regarded as beyond all therapeutic possibilities. Liver metastases were diagnosed first. Some time later a breast carcinoma was detected which was suggested to be the primary malignancy. Since high ER-values were demonstrated in the breast carcinoma, anti-estrogen therapy was given on trial. After 3 mo the tumor mass in the liver had drastically diminished and today, more than 4 yr after diagnosis, the patient is free from symptoms and doing excellently. A retrospective, microspectrophotometric DNA analysis in both the breast carcinoma and the liver metastasis showed DNA distribution patterns with nearly all the carcinoma cells exhibiting DNA values in the normal diploid region. This type of DNA profile has previously been shown to be correlated with good prognosis. We conclude that quantitative parameters such as DNA- and ER-content can give prognostic and therapeutic information over and above that furnished by clinical stage and morphological criteria. (Author abstract) (15 Refs)

7. HISTOPATHOLOGICAL MALIGNANCY GRADING AND FAMILIALITY IN AN UNSELECTED SERIES OF 1303 WOMEN WITH BREAST CARCINOMA.

Adami HO, Jung B, Lindgren A, Rimsten A
(c/o Rimsten) Dept. Surgery, Univ. Hosp., S-750 14 Uppsala, Sweden
Ann Clin Res; 14(2):76-82 1982

The Ackerman system for malignancy grading was used to study the distribution of different malignancy grades in an unselected series of 1,303 women with breast cancer. The relationship between this system and the degree of differentiation, cell polymorphism, and the presence of axillary node involvement with and without periglandular growth was studied. Type I cancers (noninvasive intraductal and lobular in situ carcinomas) were found in 39 patients, Type II (invasive, rarely metastasizing) in 75, Type III-1 (invasive, moderately metastasizing ordinary invasive ductal or lobular carcinoma) in 793, Type III-2 (intraductal or lobular in situ carcinoma with areas of invasion) in 95, and Type IV (invasive, highly metastasizing) in 301. Type III-1 predominated in all age groups. Ductal cancers comprised 91% of all cancers. Axillary lymph nodes were available for examination in 844 cases: no lymph node metastases were found in Types I and II; while 2% of Type III-2, 40% of Type III-1, and 77% of Type IV had metastases. Periglandular growth was observed only in 9% of Type III-1 and 59% of Type IV. Familial occurrence of breast cancer was confirmed in 19% of the patients. Distribution of malignancy grades, degree of differentiation, grade of cell polymorphism, and frequency of lymph node metastases had no correlation with familial tendencies. (23 Refs)

8. SITE SIZE AND SIGNIFICANCE OF PALPABLE METASTATIC AND 'REACTIVE' NODES IN OPERABLE BREAST CANCER.

Black RB, Steele RJ, Collins WC, Forrest AP
Dept. Surgery, Univ. Adelaide, Queen Elizabeth Hosp., Woodville 5011, Australia
Clin Oncol; 8(2):127-135 1982

A study was undertaken to determine the size and nature of palpable axillary lymph nodes in 50 patients undergoing mastectomy for breast cancer. Three hundred and fifty nodes (1-18 per patient, median 6) were weighed, measured, and their position mapped with respect to the primary tumor. Each was examined histologically, and classified: (a) unstimulated; (b) 'metastatic' (gross, microscopic); (c) 'reactive' viz sinus histiocytosis; lymphocyte predominance; germinal center predominance; or, (d) fatty replacement or lymphocyte depletion. All node categories (b) (c) and (d) were larger than unstimulated nodes (max diameter 0.1-2.0 cm, median 0.8 cm, wt 0. 2-0.88 g, median 0.11 g). Patients with palpable nodes had at least one in the axillary node sample which exceeded 1.5 cm diameter and/or 1.0 g in wt. Above these limits metastatic nodes were usually palpable (12/15, 11/12); 'reactive' nodes were often palpable (5/15, 5/8); and fatty nodes rarely, if ever, palpable (1/20, 1/13). Nodes with metastatic deposits or germinal center predominance were lower in the axilla than nodes showing other features. From their relative positions it seems more likely that the less favorable germinal center predominance is a 'reaction' to the primary tumor than either sinus histiocytosis or lymphocyte predominance. (Author abstract) (16 Refs)

9. CORRELATION OF MEAN NUCLEAR AREA WITH ESTROGEN RECEPTOR CONTENT IN ASPIRATION CYTOLOGY OF BREAST CARCINOMA.

Mossler JA, McCarty KS, Woodard BH, Mitchener LM, Johnston WW
(c/o McCarty) Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Acta Cytol (Baltimore); 26(4):417-421 1982

Thin needle aspirates of 42 consecutive breast carcinomas were obtained at the time of excisional biopsy. Nuclear diameters of 100 cells from each case were measured, and the nuclear areas were calculated. The concomitantly acquired histologic sections were reviewed and assigned a histologic grade according to the National Surgical Adjuvant Breast Project protocol no 4. Estrogen receptor (ER) content was analyzed by both the DCCA and SDGA techniques. The ER content of each case was then compared to both the mean nuclear area of the cells on the cytologic smears and the histologic grade. All 16 cases with mean nuclear areas of less than 60 sq um contained significant levels of ER (greater than 10 fmol/mg protein), as did 6 of 11 cases with nuclei between 60 and 90 sq um. Only 5 of 15 cases with nuclei larger than 90 sq um contained significant ER levels. Comparison of the sensitivity, specificity and predictive values of both techniques suggests that a quantitative assessment of nuclear area in cytologic thin needle aspirates correlates more closely with ER content then does histologic grading. (Author abstract) (16 Refs)

10. ASPIRATION CYTOLOGY IS SUPERIOR TO TRU-CUT NEEDLE BIOPSY IN ESTABLISHING THE DIAGNOSIS OF CLINICALLY SUSPICIOUS BREAST MASSES.

Shabot MM, Goldberg IM, Schick P, Nieberg R, Pilch YH
Los Angeles County Harbor/Univ. California Los Angeles Medical Center, 1000 West Carson St., Torrance, CA, 90509
Ann Surg; 196(2):122-126 1982

Eighty-one consecutive patients with breast masses clinically suspicious for malignancy were evaluated prospectively. There were 31 benign lesions and 50 malignancies. Clinical diagnosis was correct in 85% (2.5% false negative, 12.5% false positive). Mammography was diagnostic in 52.8% (31.5% false negative, 15.7% false positive). Needle biopsy was accurate in 78.9% (21.1% false negative, 0% false positive). Aspiration cytology was diagnostic in 96.2% (3.8% false negative, 0% false positive). Statistical comparison of all four tests revealed that aspiration cytology was slightly more accurate than physical examination for all lesions ($p = 0.07$), but significantly more accurate for benign lesions ($p = 0.005$). Overall, aspiration cytology was significantly more accurate than mammography ($p = 0.000001$) and needle biopsy ($p = 0.008$). Only one minor complication, a superficial infection, occurred with aspiration cytology and needle biopsy. Thin-needle aspiration cytology is a benign procedure that appears to be superior to physical examination, mammography, and needle biopsy in establishing the diagnosis of clinically suspicious breast masses. (Author abstract) (17 Refs)

BIOCHEMICAL AND BIOLOGIC MARKERS OF BREAST CANCERS

11. ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER IN BLACK AMERICANS. CORRELATION OF RECEPTOR DATA WITH TUMOR DIFFERENTIATION.

Mohla S, Sampson CC, Khan T, Enterline JP, Leffall L, White JE, Gabriel BW, Hunter JB
Howard Univ. Cancer Center, 2041 Georgia Ave., Northwest, Washington, DC, 20060
Cancer; 50(3):552-559 1982

It has been observed that 60-70% of breast cancer patients have estrogen (ER) and that nearly two-thirds of such patients respond favorably to endocrine therapy. Cytosolic ER and progesterone receptors (PgR) have been evaluated in the current study, among 146 black women with breast cancer in order to determine whether the distribution of ER and PgR differs from the national normal. The results showed following trends that were similar to reports from other institutions: (1) postmenopausal patients and primary tumors showed higher ER positivity than premenopausal patients and metastatic sites, respectively; (2) a significant correlation between the ER positivity and tumor grade; and (3) a higher PgR positivity in ER-positive patients than in ER-negative patients. However, statistically significant differences were observed in three parameters when compared to reports from other institutions on white patients: (1) a low incidence of ER-positive (46%) and high incidence of ER-negative (42%) tumors; (2) a higher incidence of poorly differentiated (55.5%) and a lower incidence of well differentiated (5.5%) tumors; tumor grade was independent of age, menopausal status, histopathology and stage; and (3) a higher percentage of patients discovered at a more advanced stage of the disease. The clinical implications of these results in explaining the relatively poorer survival of black women with breast cancer compared to whites is discussed. Whether this high incidence of PD tumors and thus a high incidence of ER negativity is due to ethnic differences and/or environmental and other factors remains to be elucidated. (Author abstract) (48 Refs)

12. PLOIDY, PROLIFERATIVE ACTIVITY AND ESTROGEN RECEPTOR CONTENT IN HUMAN BREAST CANCER.

Raber MN, Bargolie B, Latreille J, Bedrossian C, Fritsche H, Blumenschein G
Oncology Div., Univ. Texas Medical Sch., 6431 Fannin St., Houston, TX, 77030
Cytometry; 3(1):36-41 1982

DNA flow cytometry was used in the analysis for ploidy and proliferative activity in 80 patients with breast cancer (43 primary, 37 metastatic). Estrogen receptor (ER) content was examined in 61 tumors (40 primary, 21 metastatic). Ploidy analysis showed that 68/80 tumors (65%) were hyperdiploid. A unimodal ploidy distribution was seen in 73 tumors; in 7 there were two distinct aneuploid subpopulations. The degree of ploidy abnormality was not related to extent of disease or menopausal status but was higher in poorly differentiated tumors. There was a higher proportion of diploid tumors in the ER-positive group (7/31 versus 3/30 ER-negative). DNA content was constant in biopsies from multiple sites in five patients with metastatic disease and in serial biopsies over the course of the disease. Proliferative activity, as indicated by percentage of cells in the S phase, was not related to extent of disease and menopausal status. High proliferative activity was more often associated with ER-negative tumors than ER-positive tumors, although there was a wide range of values in all subgroups. There was no significant increase in proliferative activity associated with increasing number of positive nodes at time of surgery or with increasing clinical stage. It is concluded that flow cytometric analysis of cellular DNA content provides a rapid means of quantitating ploidy and proliferative activity in human breast cancer. (40 Refs)

13. RELATIONSHIP BETWEEN THE CONTENT OF ESTROGEN AND PROGESTERONE RECEPTORS AND THE PATHOLOGICAL CHARACTERISTICS IN HUMAN BREAST CANCER.

Nishimura R, Misumi A, Kimura M, Tokunaga T, Akagi M
Second Dept. Surgery, Kumamoto Univ., Sch. Medicine, 1-1-1 Honjo, Kumamoto 860, Japan
Jpn J Surg; 12(3):191-197 1982

Prognostic significance of determination of estrogen receptors (ER) and progesterone receptors (PR) was studied in 124 women (27-88 yr old) with primary breast cancer. The ER and PR were analyzed using a dextran-coated charcoal competitive protein binding assay. The mastectomy specimens were measured, and the histological examination of primary tumors and of the axillary lymph nodes was performed. Of 124 tumors, 58.9% were ER-positive and 33.1% were PR-positive. The ER and PR contents were not correlated with the menopausal status, size of the tumor, involvement of the axillary lymph nodes, or histological type of the tumor. The ER and PR status showed significant correlation with the histological grade: 78.2% of well differentiated Grade I tumors and 60.0% of Grade II tumors were ER-positive, compared with 27.5% of Grade III tumors. Correspondingly, 47.8% of Grade I tumors and 35.0% of Grade II tumors were PR-positive, compared with 6.8% of Grade III tumors. The tumors with little lymphoid infiltration had higher ER and PR levels than the tumors with abundant lymphoid infiltration. (26 Refs)

14. SHORT-TERM CULTURE OF HUMAN BREAST CANCER: IN VITRO EFFECTS OF HORMONES RELATED TO PATIENT RESPONSE.

Poulsen HS, Bichel P, Andersen J
Inst. Cancer Res., Radiumstationen, 44 Norrebrogade, DK-8000 Arahus C, Denmark
Br J Cancer; 46(1):67-74 1982

Breast-cancer tissue from 60 patients was tested for estrogen and testosterone sensitivity in vitro by measuring [3H]-dT incorporation in tissue fragments at various times during 48 hr culture. Hormone sensitivity in test culture was determined as an increase or decrease in dT uptake. In vitro cultures of breast-cancer tissue demonstrate that some tumors are hormone-sensitive and others hormone-insensitive, but it cannot be predicted whether cell proliferation is stimulated or inhibited by hormone treatment. The data were related to the clinical stage of the patients, menopausal status, and the degree of anaplasia of the tumors tested. No correlation was observed between these parameters and in vitro hormonal sensitivity. However, when related to the response of patients to various kinds of hormonal treatment, a significant positive correlation was obtained. (Author abstract) (22 Refs)

15. ESTROGEN RECEPTORS IN HUMAN BREAST CANCER. I. SPECIFICITY OF THE HISTOCHEMICAL LOCALIZATION OF ESTROGEN RECEPTORS USING AN ESTROGEN-ALBUMIN FITC COMPLEX.

van Marle J, Lindeman J, Ariens AT, Labruyere W, Van Weeren-Kramer J
Pharmacological Lab., Univ. Amsterdam, Polderweg 104, NL-1093 KP Amsterdam, The Netherlands
Virchows Arch [Cell Pathol]; 40(1):17-25 1982

An investigation of the specific localization of estrogen receptors in frozen sections of mammary tumors using an estrogen-BSA-FITC complex is presented. The results are discussed in relation to the existing literature. Although the fluorescence is certainly not due to interaction with Type I receptors, the reaction is not as non-specific as is suggested sometimes in the literature. It is likely that Type II receptors are involved, which are probably localized at the same site as Type I receptors. (Author abstract) (23 Refs)

16. ESTROGEN RECEPTORS IN HUMAN BREAST CANCER. II. CORRELATION BETWEEN THE HISTOCHEMICAL METHOD AND BIOCHEMICAL ASSAY.

Meijer CJ, Van Marle J, Persijn JP, Van Niewenhuizen W, Baak JP, Boon ME, Lindeman J
Dept. Pathology, S.S.D.Z., Reynier de Graefweg 7, NL-2625 AD Delft, The Netherlands
Virchows Arch [Cell Pathol]; 40(1):27-37 1982

The present study defines criteria for determining the presence of estrogen-receptors in human breast carcinomas demonstrated by a histochemical assay using 17beta-estradiol-carboxymethyl-oxim-bovine serum albumen-FITC. The criteria were: (1) the percentage of cells showing fluorescence; (2) the intensity of the fluorescence observed, and (3) the percentage of epithelial structures in tissue specimens. Using these predefined criteria in 132 human breast carcinomas a 91.6% agreement was found between the results of the histochemical assay and those of the biochemical Charcoal method. The main causes of disagreement (7 of the 11 cases) were sampling errors between the tissue specimens used for the histochemical and biochemical assay, and an insufficient percentage of epithelial structures (less than 15%) to allow biochemical identification of estrogen receptor activity. In the hands of pathologists with experience in the field of histochemistry this histochemical assay may be the method of choice for the assessment of estrogen receptors. (Author abstract) (16 Refs)

17. BIOLOGICAL MARKERS IN HUMAN BREAST CARCINOMA.

Walker RA
Dept. Pathology, Leicester Royal Infirmary, Clinical Sciences Building, P.O. Box 65, Leicester LE2 7LX, England
J Pathol; 137(2):109-117 1982

Serial sections of a group of breast carcinomas excised from 75 patients were examined by the immunoperoxidase method for the presence of five potential biological markers: two appropriate to the breast (alpha lactalbumin and secretory immunoglobulin A), two placental proteins (alpha subunit of human chorionic gonadotropin and betal pregnancy specific glycoprotein), and one oncofetal protein (carcinoembryonic antigen). The incidences for the individual antigens and the number of carcinomas containing none, one, or more antigens are presented. A positive staining reaction for different antigens could be seen in similar areas in several carcinomas. When alpha subunit and betal pregnancy specific glycoprotein were demonstrated within the same carcinoma it was mainly within the same areas, although the number of positive cells varied. Lactalbumin was essentially identifiable in separate areas from other antigens when present in the same tumor. Tumors with three or more antigens detectable tended to be well or moderately differentiated, with only 10% of poorly differentiated carcinomas being in this category. Carcinomas with no detectable markers were more likely to have no evidence of lymph node metastasis, with the converse applying to the tumors with four or five markers. (12 Refs)

CLINICAL IMMUNOBIOLOGY OF BREAST CANCERS

18. PREOPERATIVE AND POSTOPERATIVE REACTIVITY OF BREAST CANCER PATIENTS AGAINST TUMOR-ASSOCIATED ANTIGENS AND HEP IN THE MACROPHAGE-ELECTROPHORETIC-MOBILITY (MEM) TEST.

Ladusch M, Schaffner H, Ullmann L, Littmann M, Reimann S, Gindl P, Ambrosius H
Sektion Biowissenschaften, Karl-Marx-Universitat, Talstrasse 33, DDR-7010 Leipzig, E. Germany
Arch Geschwulstforsch; 52(6):469-478 1982

Fifty women, including 27 with breast cancer (BC) and 23 with benign diseases of the breast, were testes preoperatively by the macrophage-electrophoretic-mobility (MEM) test. Patients with BC included five with a second BC occurring several yr after ablation of the contralateral breast. Patients with benign diseases included 21 with benign tumors (16 fibrocystic mastopathies, 2 fibroadenomas, 1 foam-cell granuloma, 1 intracanalicular papilloma, and 1 lipoma). Patients with BC were tested 4-7 days, 5-8 wk, and 11-20 wk postoperatively. In all tests, MEM tests were conducted in the presence of human encephalitogenic protein (HEP), 3 M KCl extract of BC tissue, or 3 M KCl extract of renal carcinoma (RC). A total of 289 tests were conducted on 102 blood samples from 50 patients. Preoperative diagnosis by the MEM test had an accuracy of 89%, a sensitivity of 86%, and a selectivity of 91% with BC extract; with HEP the accuracy was 86%, the sensitivity 75%, and the selectivity 95%. With RC extract, positive results were obtained in only 3% of tests; the selectivity was 97%, indicating that the MEM test is organ-specific. In BC patients, reactivity to HEP and BC extract was not immediately affected by surgery. Reactivity declined sharply 5-8 wk after surgery. In some patients reactivity later increased, suggesting a recurrence of BC. Inhibition of lymphocytic migration showed two nonoverlapping groups, one with values near 0% and one with values near 10%. The MEM test using HEP or BC extract as the antigen is evidently useful for differentiation of benign and malignant breast disease and for follow-up of BC. (32 Refs) (In GER)

BREAST CANCER THERAPY (SURGERY, IRRADIATION, DRUG, HORMONE, IMMUNOLOGY)

19. TAMOXIFEN, AMINOGLUTETHIMIDE AND DANAZOL: EFFECT OF THERAPY ON HORMONES IN POST-MENOPAUSAL PATIENTS WITH BREAST CANCER.

Coombes RC, Powles TJ, Rees LH, Ratcliffe WA, Nash AG, Henk M, Ford HT, Gazet JC, Neville AM
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 46(1):30-34 1982

Gonadotrophins, estradiol, androstenedione, testosterone and dehydroepiandrosterone sulfate (DHAS) were measured sequentially in 72 patients with advanced breast cancer receiving endocrine therapy of various types. Tamoxifen significantly reduced gonadotrophins but did not effect other hormones. Danazol also reduced gonadotrophins. Aminoglutethimide (AGT) reduced estradiol and DHAS but had no effect on gonadotrophins. The effects of administering tamoxifen, AGT and danazol together (TAD) were therefore examined. This combination reduced gonadotrophins, estradiol and DHAS, but no further than tamoxifen and AGT alone. The degree and duration of hormone suppression were similar in both responders and non-responders to tamoxifen, AGT or TAD, though patients responding to AGT showed more complete suppression at the end of the course of treatment, perhaps because they were treated longer. On relapse, adequate gonadotrophin and steroid suppression was demonstrated in patients receiving tamoxifen and AGT, respectively. We conclude that (a) response to endocrine therapy is unlikely to be related to the degree of endocrine suppression produced by the therapy; (b) combination endocrine therapy does not further reduce serum-hormone concentrations and (c) relapse is unlikely to be due to escape from the hormone-inhibitory effects of endocrine agents. (Author abstract) (11 Refs)

20. COMBINATION CHEMOTHERAPY (CMFVP) VERSUS L-PHENYLALANINE MUSTARD (L-PAM) FOR OPERABLE BREAST CANCER WITH POSITIVE AXILLARY NODES. A SOUTHWEST ONCOLOGY GROUP STUDY.

Glucksberg H, Rivkin SE, Rasmussen S, Tranum B, Gad-el-Mawla N, Costanzi J, Hoogstraten B, Athens J, Maloney T, McCracken J, Vaughn C
Operations Office, Southwest Oncology Group (SWOG-7436), 4450 Medical Dr., San Antonio, TX, 78229
Cancer; 50(3):423-434 1982

The Southwest Oncology Group in a prospective randomized study compared 1 year of adjuvant combination chemotherapy with continuous CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone) to 2 years of intermittent L-PAM (L-phenylalanine mustard) in women with operable breast cancer with histologically positive axillary lymph nodes. In fully evaluable patients with a 42-mo median and 30-mo minimum follow-up, treatment failures have occurred in 26% of 145 receiving CMFVP and 47% of 167 women given L-PAM ($p = 0.002$). Disease-free survival times were significantly longer with CMFVP than with L-PAM in the following subgroups: premenopausal women ($p = 0.002$), postmenopausal women ($p = 0.002$), women with 1-3 involved axillary nodes ($p = 0.003$), and women with four or more involved axillary nodes ($p = 0.002$). CMFVP was effective in pre- and postmenopausal women. There is a significant difference in survival in favor of CMFVP compared to L-PAM ($p = 0.005$). The life table estimates of survival at 42 mo are 86% for women on the CMFVP treatment arm and 73% for women on the L-PAM treatment arm. There was no correlation between the interval from mastectomy to onset of chemotherapy (between 1 and 6 wk) and recurrence rates. Acute toxicity with both treatment arms was moderate and reversible. These results show that continuous CMFVP is superior to intermittent L-PAM in decreasing recurrences and increasing survival in both pre- and postmenopausal women with operable breast cancer with histologically involved axillary nodes. (Author abstract) (25 Refs)

21. BREAST CANCER AND ESTROGEN REPLACEMENT THERAPY.

Hulka BS, Chambless LE, Deubner DC, Wilkinson WE
Dept. Epidemiology, Univ. North Carolina, Rosenau Hall 201 H, Chapel Hill, NC, 27514
Am J Obstet Gynecol; 143(6):638-644 1982

Concern over the possible effect of estrogen replacement therapy on the subsequent development of breast cancer prompted us to compare 199 postmenopausal breast cancer patients with 451 hospital control subjects and 852 community control subjects on their prior use of estrogens. Estrogen use did not increase the breast cancer risk for women with a surgical menopause. Among women with a natural menopause, estrogens administered by all routes were associated with breast cancer risks of 1.7 or 1.8. There was no coherent pattern of changing risks with varying durations of use, different daily dosages, years since first use of estrogen, or years since most recent use. When women who usually received estrogen by injection were excluded, the risk estimates for oral estrogens were 1.3 (case subjects compared to community control subjects) and 1.2 (case subjects compared to hospital control subjects). These increases were not statistically significant. Use of injectable estrogens produced a four-fold increase in breast cancer risk among naturally postmenopausal women. (Author abstract) (14 Refs)

22. EFFECTS OF TAMOXIFEN ON THE SERUM LEVELS OF OESTROGENS AND ADRENOCORTICAL STEROIDS IN POSTMENOPAUSAL BREAST CANCER PATIENTS.

Wilking N, Carlstrom K, Skoldefors H, Theve NO, Wallgren A
Dept. Surgery II, Sabbatsberg Hosp., S-11382 Stockholm, Sweden
Acta Chir Scand; 148(4):345-349 1982

Peripheral serum levels of cortisol, dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHA-s), estradiol-17beta and total estrone were measured in 17 postmenopausal breast cancer patients and in age-matched healthy controls. In the breast cancer patients analyses were performed before and after 1, 2, 4, 8 and 12 wk of treatment with tamoxifen. Basal DHA levels were significantly higher in breast cancer patients than in controls; otherwise no significant differences were noted. Treatment with tamoxifen resulted in significantly elevated levels of cortisol throughout the period of treatment; this effect was probably solely due to an increase in transcortin levels. A transient but significant elevation in total estrone, probably related to liver function, was observed after 1 wk of treatment. No significant effects of tamoxifen were noted on serum DHA, DHA-s or estradiol-17beta. The results indicate that tamoxifen does not affect the adrenocortical steroid biosynthesis in postmenopausal women. The estrogenic effects of tamoxifen upon FSH, prolactin and the estrogen induced Pregnancy Zone Protein (PZP) in postmenopausal women, described in a previous communication from this group, are probably not due to any increase in the serum estrogens since this increase is transient and hardly impressive. The weak estrogenic effects of the tamoxifen-receptor complex itself may thus be sufficient to produce net estrogenic effects in subjects with low endogenous estrogens such as postmenopausal women. (Author abstract) (36 Refs)

23. BRACHIAL PLEXOPATHY AFTER RADIATION THERAPY FOR TREATMENT OF BREAST CANCER (MEETING ABSTRACT).

Fields RS, Glass P, Spanos WJ, Montague ED
University of Texas at Houston, M. D. Anderson Hospital, Houston, TX, 77030
Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

An analysis of patients treated for primary breast cancer with radiation therapy, with or without surgery, has been made to determine the incidence of brachial plexopathy. Only 16 patients have developed this complication out of approximately 4,000 patients treated since 1955. The risk rate has been determined after radiation therapy alone (1.1%), radiation prior to (.2%)or after (.4%) a mastectomy, and following a segmental breast resection (.3%). The level of neuropathy was graded (1 to 3) relative to sensory loss or partial or complete motor loss respectively. The grade of neuropathy correlated with supraclavicular and axillary tumor dose, dosimetric technique, use of chemotherapy, latency period after radiation, and other factors. Of the 16 patients, 14 had identifiable factors which may have led to the complication including axillary tumor dose greater than 5750 rad, altered fractionation, chemotherapy, or history of systemic lupus erythematosis. Although the risk of brachial plexus injury is low, suggestions are made on how to reduce it even further. (no Refs)

24. CONCOMITANT EXTERNAL BEAM RADIATION AND ADJUVANT CHEMOTHERAPY IN THE PRIMARY MANAGEMENT OF BREAST CANCER (MEETING ABSTRACT).

Botnick L, Come S, Rose C, Goldstein M, Lange R, Tischler S, Schnipper L, Harris J, Hellman S
Joint Center for Radiation Therapy, 50 Binney St., Boston, MA, 02115
Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

Recently women with breast cancer and pathologically positive nodes, are routinely placed on adjuvant chemotherapy. Studies have suggested that immediate post-operative chemotherapy and the ability to deliver 85% of the prescribed dose are factors which are associated with increased disease-free survival. Forty-two women candidates for primary radiation and adjuvant chemotherapy were treated between May, 1980 and November, 1981. Axillary node status was determined by a sampling procedure. Thirteen women were clinical stage I, 24 stage II, 3 stage III, and 2 stage IV. Forty-one of 42 patients were treated with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) while 1 patient received CMF-VP (vincristine, prednisone). Chemotherapy was initiated as early as 2 days after the axillary sampling. The dose delivered to the breast and IM nodes was 4600-5000 rad and to the axilla was 4600-6000 rad. An additional 1600-2500 rad was delivered to the region of breast excision by either an interstitial implant or electron boost (5 patients). The interstitial implant was done at the time of excision when feasible. During radiation, all patients received greater than 90% of their prescribed chemotherapeutic dose. Of the 12 patients that completed their adjuvant chemotherapy 10 have received greater than 90% of their prescribed dose without time delay. Though the acute skin reaction during radiation was exacerbated, careful attention to the timing of radiation in relation to the chemotherapy cycle ameliorated these problems. In summary, the use of concurrent chemotherapy and irradiation allows for the initiation of drugs shortly after axillary sampling and prior to the initiation of external radiation. Delivery of the full prescribed dose of chemotherapy is usual and the overall treatment is not prolonged. (no Refs)

REHABILITATION ASPECTS OF BREAST CANCER MANAGEMENT

25. THORACO-ABDOMINAL AND THORACOEPIGASTRIC FLAPS: ALTERNATIVES TO SKIN GRAFTING AFTER MASTECTOMY.

Leinster SJ, Webster DJ
Univ. Dept. Surgery, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales
Clin Oncol; 8(2):145-148 1982

Thoraco-abdominal and thoracoepigastric flaps are reliable methods of closing skin defects resulting from mastectomy or excision of the chest wall. We have used 17 thoraco-abdominal and 10 thoracoepigastric flaps without any major problems. The final cosmetic result is good and the patient retains full function of the arm. The technique allows sacrifice of large amounts of skin, while providing a better final cosmetic result than obtained with skin grafts, and allowing retention of full function of the arm. (Author abstract) (6 Refs)

26. IMMEDIATE BREAST RECONSTRUCTION AFTER MASTECTOMY USING A RECTUS ABDOMINIS MYODERMAL FLAP WITHOUT AN IMPLANT.

Drever JM, Hodson-Walker NJ
Ste. 322, 89 Humber College Blvd., Rexdale, Ont. M9B 4B8, Canada
Can J Surg; 25(4):429-431 1982

In the author's opinion there is no physical reason for a waiting period after total mastectomy before the breast is reconstructed. If the duration of the patient's survival is limited, the sooner the breast is reconstructed the better. The authors do not use silicone implants that may be blamed for the appearance of recurrent tumor but reconstruct the breast with a vertical rectus abdominis myodermal flap immediately after the mastectomy. The flap is an island of skin, fat and muscle extending from the xiphoid to the pubis; it receives its blood supply from the perforators of the superior-inferior epigastric vascular axis on the same side as the mastectomy. The rectus abdominis muscle is the pedicle and carrier of the vessels that feed the ellipse of skin. The flap is doubled on itself and thus forms a cone. It is then passed into the breast area by undermining the intervening bridge of skin. Nipple and areola are grafted onto the flap. This operation enables a wide resection, so that the principles of cancer management are not compromised. (Author abstract) (11 Refs)

27. BREAST AESTHETICS WHEN RECONSTRUCTING WITH THE LATISSIMUS DORSI MUSCULOCUTANEOUS FLAP.

Millard DR
1444 N.W. 14th Ave., Miami, FL, 33125
Plast Reconstr Surg; 70(2):161-172 1982

The main merits of the latissimus dorsi musculocutaneous flap in breast reconstruction are the addition of a muscle as well as a skin component and the speed and efficiency of the reconstruction. Seven salient points in this technique have been discussed and emphasis has been placed on the ideal shape of the skin island. Previously, the shape has been consistently a stereotypical ellipse, but the possibilities of adapting the shape to the specific donor scar and contour of the opposite breast may offer possibilities and has been outlined with drawings and demonstrated on patients. (Author abstract) (10 Refs)

SELECTED ASPECTS OF PRE-CLINICAL BREAST CANCER RESEARCH (CELL BIOLOGY, IMMUNOLOGY, PHARMACOLOGY)

28. PURIFIED MEMBRANE FRACTIONS FROM MAMMARY TUMOR CELLS ELICIT BIOLOGICAL REACTIVITY IN IN VITRO CELL-MEDIATED IMMUNE REACTIONS.

Buessow SC, Caldwell K, Fletcher MA, Lopez DM
Dept. Microbiology, Univ. Miami Sch. Medicine, Miami, FL, 33101
Eur J Cancer Clin Oncol; 18(6):595-604 1982

Lithium chloride (LiCl) aggregation followed by centrifugation through a sucrose step gradient was used to obtain purified plasma membranes from two sublines of mouse mammary adenocarcinoma. These two tumor lines were chemically induced by treatment of a hyperplastic nodule with 7,12-dimethylbenzanthracene (DMBA). One line, D1-DMBA-3, has been found to be immunogenic to the host of origin, while the other, D1-DMBA-2, does not elicit specific tumor immunity as previously tested in in vivo and in vitro immune reactions. The purified membrane fractions were assayed for protein, DNA and sialic acid content as well as enzymatic markers of membrane purity. When tested in blastogenesis and cytotoxicity reactions, membrane-containing fractions from the D1-DMBA-3 immunogenic tumor were found to be stimulatory to spleen cells of D1-DMBA-3 tumor bearers over a 10-fold protein concentration. Spleen cells from normal mice do not respond in these reactions to the various tumor fractions. No reactivity was observed when non-membrane-containing preparations were used as stimuli in the cell-mediated immune reactions. The specificity of these reactivities was further demonstrated by the lack of responses when fractions from the non-immunogenic D1-DMBA-2 tumor were tested in parallel in our in vitro assay. The data presented indicate that the procedure employed is useful for the isolation of membrane-associated, tumor-specific antigens which can be easily quantitated and still retain biological activity in in vitro tests of cell-mediated immunity. (Author abstract) (41 Refs)

29. REGRESSION OF CANINE MAMMARY CARCINOMA AFTER IMMUNOADSORPTION THERAPY.

Holohan TV, Phillips TM, Bowles C, Deisseroth A
(c/o Bowles) Hazelton Lab America, Inc., 9200 Leesburg Pike, Vienna, VA, 22180
Cancer Res; 42(9):3663-3668 1982

The plasma of dogs afflicted with mammary carcinoma was perfused through chambers bearing Staphylococcus aureus Cowan Strain 1 in an attempt to remove tumor-promoting, immunosuppressive immune complexes from the peripheral blood of these animals. In this canine model of spontaneous mammary carcinoma, reduction of breast and/or soft-tissue tumor (posttreatment size equal to 0 to 50% of pretreatment tumor size) was observed in 5 of the 10 animals so treated. Immune complexes capable of blocking lymphocytotoxicity were measured pre- and postimmunoadsorption; removal was more efficient in the five responders (4 of 6 complexes) than in nonresponders (1 of 10 complexes), although statistical significance was not attained. The reduction of tumor size seen in soft-tissue sites was not always accompanied by a similar reduction of tumor size in visceral sites, and surgical resection of residual soft-tissue tumor nodules remaining after immunoadsorption treatment was required to achieve a complete response in two responding animals. No significant decrease in tumor size was observed in the control group, perfused without immunoadsorbent, nor in five additional tumor-bearing animals infused with normal dog plasma which had been passed through S aureus Cowan Strain 1-containing chambers. These data indicate that immunoadsorption of tumor-bearing host plasma can result in reduction in size of canine mammary adenocarcinoma but that the response is dependent on the site of the tumor (sc versus visceral) and may require utilization of other modalities to achieve a complete disappearance of the tumor. (Author abstract) (31 Refs)

30. SYNTHESIS, RETENTION, AND BIOLOGICAL ACTIVITY OF METHOTREXATE POLYGLUTAMATES IN CULTURED HUMAN BREAST CANCER CELLS.

Jolivet J, Schilsky RL, Bailey BD, Drake JC, Chabner BA
Clinical Pharmacology Branch, Div. Cancer Treatment, NCI, Bethesda, MD, 20205
J Clin Invest; 70(2):351-360 1982

To determine the pharmacologic importance of methotrexate (MTX) polyglutamates, we examined the formation, retention, and effect of these metabolites in cultured human breast cancer cells. Two cell lines converted the drug to gamma-polyglutamate derivatives in a dose- and time-dependent reaction. After 24-hr incubations with 2uM MTX, polyglutamates of two to five amino acids in length accounted for 55.4% of intracellular drug in MCF-7 cells and 87.6% of drug in ZR-75-B cells. MDA-231 cells showed lesser accumulation of MTX, and only 32% of the intracellular drug was in the form of polyglutamates, a difference that could only partially be explained by decreased ability of these cells to take up free drug from the medium. When MCF-7 and ZR-75-B cells containing polyglutamates were transferred to drug-free medium for 24 hr, 22 and 51% of the total intracellular drug were, respectively, retained in each cell line. The loss of intracellular drug was primarily accounted for by disappearance of parent compound and polyglutamates containing 1-3 additional glutamyl residues. The rates of disappearance from cells decreased with increasing glutamyl chain length. The retention of MTX polyglutamates in the two cell lines in excess of dihydrofolate reductase binding capacity led to prolonged inhibition of thymidylate synthesis and loss of cell viability after removal of extracellular

MTX. These studies demonstrate that polyglutamate formation allows a prolonged retention of drug in a noneffluxable form and prolonged inhibition of both thymidylate synthesis and cell growth following removal of extracellular drug. (30 Refs)

31. IGA CONTAINING IMMUNE COMPLEXES IN DOGS BEARING A SPONTANEOUS MAMMARY ADENOCARCINOMA.

Balint J, Nagai T, Ikeda Y, Meek K, Terman DS
Dept. Medicine, Baylor College Medicine, Houston, TX, 77030
Clin Exp Immunol; 49(2):433-440 1982

Sera from dogs with mammary adenocarcinoma were assessed for the presence of immune complexes (IC) and the physicochemical composition of these complexes was investigated. Employing 125I-anti-canine IgG as indicator, elevated levels of C1q binding IgG were detected in sera of dogs with mammary adenocarcinoma. Polyacrylamide gel electrophoresis (PAGE) analysis of IC isolated by G-200 fractionation and protein A affinity chromatography revealed the presence of a dense polypeptide band corresponding to the alpha chain of IgA which was present in the mammary adenocarcinoma sera but not in normal dog sera or sera from dogs with other tumors. Employing monospecific radiolabeled anti-canine IgA as indicator in solid phase C1q binding radioimmunoassays, significantly elevated levels of C1q binding IgA were detected in five of eight mammary adenocarcinoma sera but not in sera of normal dogs or other tumor bearing dogs (p less than 0.05). Sera from mammary adenocarcinoma bearing dogs treated with 5% polyethylene glycol (PEG) and subjected to sucrose density gradient ultracentrifugation revealed IgA containing IC in fractions greater than 7S to greater than 19S. Findings suggest that IC are present in sera of dogs with mammary adenocarcinoma and that IgA is a major and unique component of these complexes and, hence, may play a significant role in the development and evolution of the canine immune response to mammary adenocarcinoma. (Author abstract) (24 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Adami HO 7
Akagi M 13
Ambrosius H 18
Andersen J 14
Ariens AT 15
Athens J 20
Auer GU 6
Azavedo E 6
Baak JP 16
Bailey BD 30
Balint J 31
Bargolie B 12
Bedrossian C 12
Bichel P 14
Black RB 8
Blomstedt B 6
Blumenschein G 12
Boon ME 16
Botnick L 24
Bowles C 29
Braun-Munzinger 5
Buessow SC 28
Caldwell K 28
Carlstrom K 22
Chabner BA 30
Chambless LE 21
Collins WC 8
Come S 24
Coombes RC 19
Costanzi J 20
Curtis AC 2
Deisseroth A 29
Deos PH 4
Deubner DC 21
Drake JC 30
Drever JM 26
Enterline JP 11
Fields RS 23
Filzmayer P 5
Fletcher MA 28
Ford HT 19
Forrest AP 8
Fritsche H 12
Gabriel BW 11
Gad-el-Mawla N 20
Gazet JC 19
Gindl P 18
Glass P 23
Glucksberg H 20
Goldberg IM 10
Goldstein M 24
Hancock JR 2
Harris J 24
Harter G 5
Hellman S 24
Henk M 19
Heslinga JM 3
Hodson-Walker N 26
Holohan TV 29
Hoogstraten B 20
Hulka BS 21
Hunter JB 11
Ikeda Y 31
Johnston WW 9
Jolivet J 30
Jung B 7
Khan T 11
Kimura M 13
Kobayashi T 1
Labruyere W 15
Ladusch M 18
Lange R 24
Latreille J 12
Leffall L 11
Leinster SJ 25
Lindeman J 15
Lindeman J 16
Lindgren A 7
Littmann M 18
Lochbuhler H 5
Lopez DM 28
Maloney T 20
McCarty KS 9
McCracken J 20
Meek K 31
Meijer CJ 16
Millard DR 27
Miller S 2
Misumi A 13
Mitchener LM 9
Mohla S 11
Montague ED 23
Mossler JA 9
Nagai T 31
Nash AG 19
Neville AM 19
Nieberg R 10
Nishimura R 13
Norris HJ 4
Pauwels EKJ 3
Persijn JP 16
Phillips TM 29
Pilch YH 10
Poulsen HS 14
Powles TJ 19
Queisser W 5
Raber MN 12
Rasmussen S 20
Ratcliffe WA 19
Rees LH 19
Reimann S 18
Rimsten A 7
Rivkin SE 20
Rose C 24
Sampson CC 11
Schaffner H 18
Schick P 10
Schilsky RL 30
Schnipper L 24
Shabot MM 10
Skoldefors H 22
Spanos WJ 23
Steele RJ 8
Sterns EE 2
Terman DS 31
Theve NO 22
Theve NO 6
Tischler S 24
Tokunaga T 13
Tranum B 20
Trede M 5
Ullmann L 18
Van Marle J 15
Van Marle J 16
Van Niewenhuize 16
Van Weeren-Kram 15
Vaughn C 20
Walker RA 17
Wallgren A 22
Webster DJ 25
White JE 11
Wilking N 22
Wilking N 6
Wilkinson WE 21
Woodard BH 9
Zwaveling A 3

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